S. Hrg. 99-512

SACCHARIN STUDY AND LABELING ACT AMENDMENTS OF 1985

HEARING

BEFORE THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

NINETY-NINTH CONGRESS

FIRST SESSION

ON

S. 484

TO AMEND THE SACCHARIN STUDY AND LABELING ACT

APRIL 2, 1985

Printed for the use of the Committee on Labor and Human Resources

U.S. GOVERNMENT PRINTING OFFICE
54-573 O WASHINGTON : 1986

S541-34

COMMITTEE ON LABOR AND HUMAN RESOURCES

ORRIN G. HATCH, Utah, *Chairman*

ROBERT T. STAFFORD, Vermont
DAN QUAYLE, Indiana
DON NICKLES, Oklahoma
PAULA HAWKINS, Florida
STROM THURMOND, South Carolina
LOWELL P. WEICKER, Jr., Connecticut
MALCOLM WALLOP, Wyoming
CHARLES E. GRASSLEY, Iowa

EDWARD M. KENNEDY, Massachusetts
CLAIBORNE PELL, Rhode Island
HOWARD M. METZENBAUM, Ohio
SPARK M. MATSUNAGA, Hawaii
CHRISTOPHER J. DODD, Connecticut
PAUL SIMON, Illinois
JOHN F. KERRY, Massachusetts

Ronald F. Docksai, *Staff Director*
Kathryn O'L. Higgins, *Minority Staff Director*

CONTENTS

STATEMENTS

TUESDAY, APRIL 2, 1985

Page
Arnold, Douglas, Ph.D., research scientist, Health Protection Branch, Health and Welfare Canada 90
  Prepared statement 92
Arky, Dr. Ronald, chief of medicine, Mount Auburn Hospital on behalf of the American Diabetes Association 140
  Prepared statement 141
Bakal, Abraham I., Ph.D., president, ABIC International Consultants, Inc., prepared statement 271
D'Amato, Hon. Alfonse, a U.S. Senator from the State of New York 9
Golberg, Leon, professor of community/occupational medicine, Duke University Medical Center, prepared statement 273
Graves, Florence, vice president for publications and editor of Common Cause magazine, prepared statement 297
Grassley, Hon. Charles E., a U.S. Senator from the State of Iowa, prepared statement 5
Hart, Ronald, Ph.D., Director, National Center for Toxicological Research [FDA] 62
  Prepared statement 65
Havender, William R., Ph.D., prepared statement 269
Hawkins, Hon. Paula, a U.S. Senator from the State of Florida, prepared statement 7
Jacobson, Michael F., Ph.D., executive director, Center for Science in the Public Interest 151
  Prepared statement 153
Kellen, Robert H., president, Calorie Control Council, prepared statement 254
Merker, James F., executive director, American Society of Bariatric Physicians, prepared statement (with enclosure) 274
National Food Processors Association, prepared statement 264
Roberts, Howard R., Ph.D., vice president, science and technology, National Soft Drink Association 157
  Prepared statement 160
Schoenig, Dr. G.P., toxicology consultant 71
  Prepared statement 74
Stegink, Lewis, Ph.D., professor, department of biochemistry and pediatrics, University of Iowa, College of Medicine 125
  Prepared statement 127
Trowbridge, Frederick, M.D., Director, Division of Nutrition, Center for Health Promotion and Education, Centers for Disease Control 108
  Prepared statement 110
Wertheimer, Fred, president, Common Cause, prepared statement 292
Whelan, Elizabeth M., executive director, American Council on Science and Health, prepared statement 268
Wurtman, Richard J., M.D., professor of neuroendocrine regulation, Massachusetts Institute of Technology 115
  Prepared statement 119
Young, Frank, M.D., Ph.D., Commissioner, Food and Drug Administration, accompanied by Dr. Gary Flamm, Associate Director for toxicology, Center for Food Safety, FDA; Dr. Sanford Miller, Director, Center for Food Safety, FDA; and Thomas Scarlett, General Counsel, FDA 11
  Prepared statement 15

ADDITIONAL MATERIAL

Page

Articles, publications, et cetera:
- Preliminary findings of a $1.5 million epidemiological study that examined the relationship between the use of artifical sweeteners such as saccharin and cyclamate and the incidence of bladder cancer in humans, from HEW NEWS, December 20, 1979 33
- Objections of the National Soft Drink Association to a final rule permitting the use of Aspartame in carbonated beverages and carbonated beverage syrup bases and a request for a hearing on the objections 218

Questions and answers:
- Responses of Dr. Arnold to questions submitted by Senator Grassley 101
- Responses of Dr. Wurtman to questions submitted by Senator Dodd 122
- Responses of Dr. Wurtman to questions submitted by Senator Grassley 124
- Responses of Dr. Trowbridge to questions submitted by Senator Grassley 139
- Responses of Mr. Jacobson to questions submitted by Senator Grassley 156
- Responses of Dr. Roberts to questions submitted by Senator Grassley 214

SACCHARIN STUDY AND LABELING ACT AMENDMENTS OF 1985

TUESDAY, APRIL 2, 1985

U.S. Senate,
Committee on Labor and Human Resources,
Washington, DC.

The committee met, pursuant to notice, at 2:06 p.m., in room SD-430, Senator Orrin G. Hatch (chairman) presiding.

Present: Senators Hatch, Nickles, Grassley, Metzenbaum, Dodd, and Simon.

Also present: Senator D'Amato.

OPENING STATEMENT OF SENATOR HATCH

The Chairman. We are happy to welcome you all here to the Labor and Human Resources Committee saccharin hearing.

Today we are holding a full Labor and Human Resources Committee hearing on S. 484, the Saccharin Study and Labeling Act. This bill would extend the current limitation on regulatory action to ban saccharin for an additional 3-year period, through April 1988.

I believe it is clear the jury is still out on saccharin. Though it has been on the market for over 80 years and has never been shown to be a public health risk in normally consumed quantities, some studies seem to indicate that it may be a weak carcinogen in rats when administered in the very high doses used in laboratory tests. Other studies show no such link.

Pending the development of more definitive data, Congress in 1978 passed the Saccharin Study and Labeling Act, which called for studies, placed a warning on substances containing saccharin, and forbade FDA action against saccharin solely on the basis of the ambiguous information available in 1978.

Studies commissioned by FDA as a result of the act were completed in 1983, and there is significant scientific disagreement over their meaning. FDA is currently reviewing these studies, but there is no indication of when a decision might take place.

Thus, the basic challenge to saccharin's long history of safe use remains unresolved, and it is appropriate that Congress pass S. 484 and thereby continue the limited moratorium covering the use of pre-1978 data. This moratorium simply states that if FDA desires to remove saccharin from the market, it may not do so solely on the basis of the conflicting evidence available in 1978. At a minimum, it must also rely on sufficient subsequent studies.

I have no doubt that S. 484's extension serves the public interest. Saccharin remains a vitally important substance for many Americans who depend on it as a sugar substitute. Though we have developed other sweeteners, none duplicates all of the particular virtues of saccharin, and none is a complete substitute for it.

The extension recognizes the public need for saccharin while still allowing FDA to take action if necessary when adequate, consistent scientific support becomes available.

Thus, in today's hearing, we will receive testimony on the scientific and technological developments related to saccharin; on its continued use by the food, drug and cosmetic industries; and on the continued need for a limited moratorium on regulatory action to ban saccharin.

I am pleased to welcome our distinguished panels of witnesses to discuss these issues and to provide an overview of saccharin and other sweeteners from a scientific and regulatory perspective. We are going to move to those witnesses in just a minute.

At this point we will turn to Senator Metzenbaum, who I am sure has a statement. We will take his statement at this time.

Senator METZENBAUM. Thank you, Mr. Chairman.

It has been 5 years since the Senate has taken a serious look at artificial sweeteners. Since that time, much has happened.

We have had two major tests on saccharin. NutraSweet has come onto the market in a big way. Consumption in 1984 rose by 40 percent, as indicated by that chart. And cyclamate is undergoing a review which may return it to the market soon.

Some time ago, I expressed concern that we not rush forward with a 3-year extension of the moratorium on the saccharin ban without pausing to see where we are with artificial sweeteners. As a matter of fact, it should be pointed out that never before has it been proposed that there be a 3-year extension.

The first extension was 18 months; the second extension, 12 months; and the last two, 24 months each. So I am still not convinced as to why we need a 3-year extension, if at all.

I requested a hearing, and you agreed, Mr. Chairman, and I want to express my appreciation for your help and the help of your staff in scheduling this hearing.

Every year, some 68 million Americans consume more than $4 billion worth of diet soft drinks which contain saccharin and NutraSweet. Americans spend another $30 billion on so-called light foods, many of which contain these same artificial sweeteners.

The boom in sweetener consumption may well be the most significant trend to hit the food industry in the last 50 years. But market trends aren't the issue for Congress. Our issue is only one: Our issue is safety. And the law says unambiguously that safety must come before market trends, quarterly profits, or new product loyalty. If there is doubt, the law errs on the side of caution.

Let me be quite specific. The Government does not have to prove a particular food additive or artificial sweetener is harmful. The manufacturer must prove that it is safe and that there is a reasonable certainty that no harm will result from its use.

Now, that is a pretty demanding standard, but I don't think that anyone here would disagree with its intent, which is to protect ourselves, our children, and our grandchildren from harmful substances in the food supply.

Today we will focus on three sweeteners: saccharin, aspartame—better known under its brand name of NutraSweet—and cyclamate.

Saccharin, which was discovered by accident in 1879, has been the subject of controversy ever since. In 1890, France banned the substance as harmful. Eight years later—I point this out to the chairman—first France banned it, then Germany did the same; Portugal, Spain, and Hungary followed suit. We will hear from a person involved in the Canadian banning today.

But in 1907, when our leading expert on food additives urged President Theodore Roosevelt to support a ban in the United States, Teddy Roosevelt replied that as a saccharin user himself, he was convinced that "anybody who says saccharin is injurious to health is an idiot."

In 1912, however, the United States banned saccharin, only to rescind that action during World War I. In 1977, the FDA once again proposed to ban saccharin. That ban has, of course, been held in abeyance by a moratorium imposed and extended four times.

Saccharin is the most thoroughly tested food additive consumed by man, and those tests have shown saccharin causes cancer in rats. Now, what does that mean for man? The FDA in 1977 did say that if everyone in the United States drank one diet soda containing saccharin a day for a lifetime, an additional 1,200 cases of bladder cancer could result.

Our hearing today will focus on two recent studies which apparently show saccharin active as a carcinogen and a cocarcinogen at much lower levels of intake. That is disturbing, but it is not the only issue.

The other issue has to do with the matter of labeling. Now, under the law, it is required that the indication be given as to the problem on labeling; that is, what the risk is. And it specifically provides—I think I have that here somewhere, the language—the language provides, section 403 of the Federal Food, Drug, and Cosmetics Act provides that if it contains saccharin, unless, except as provided in subparagraph 2, its label and labeling bear the following statement: "Use of this product may be hazardous to your health. This product contains saccharin, which has been determined to cause cancer in laboratory animals."

Well enough. Then it goes on to say in the statute:

> Such statement shall be located in a conspicuous place in such label, and labeling as proximate as possible to the name of such food, and shall appear in conspicuous and legible type in contrast by typography, layout, and color with other printed matter on such label and labeling.

I would like to point out to you, Mr. Chairman, that that may be what the law says, but up there on that chart, you will see some labels that, unless you have extremely good eyes, and I mean better than 20/20, you won't be able to actually read the label.

The one that is the third one down—and I don't exactly know what the product is—jelly—the blue label is so dark in the printing, it is almost impossible to read. And when you try to read on almost any of the labels, whether it is the saccharin label or the

Faygo cola, you have got to have supergood eyes to be able to read it.

That is not what the statute says is required, and it occurs to me that the FDA has some responsibilities in this area to enforce the law without requiring individuals to file a complaint and go into court on a criminal basis to prosecute, but that they have some direct responsibilities to see to it that the labeling conforms with the law.

Now, cyclamate, the most popular artificial sweetener of the 1950's and 1960's, was banned in October 1969 because tests indicated that it might be a carcinogen. The FDA upheld the ban in 1980. But now, FDA is reconsidering. Why? What new evidence has become available? What about the noncancer concerns we have heard about cyclamate, that it damages the genes and causes testicular atrophy? These are the questions we hope to answer at this hearing.

And, finally, there is NutraSweet, a sugar substitute whose popularity is growing in leaps and bounds. But today we will hear from Dr. Wurtman of MIT, who believes that NutraSweet affects brain chemistry, particularly when consumed with carbohydrates.

There is also the allegation raised by Common Cause that the FDA approval process for NutraSweet was badly flawed, that it was based on Searle's testing procedure which had been severely criticized by a special task force investigation.

Mr. Chairman, I am frank to tell you that I don't know the answers to all of these questions, nor do I have my mind made up. But I believe that the questions must be pursued, and to that end, I intend to do my best today to find the answers.

Thank you, Mr. Chairman, for your courtesy and your cooperation in setting up this hearing, and I look forward to working with you to see whether or not we can bring about some piece of legislation that can be enacted before the saccharin ban extension expires which, to my understanding, is April 21.

The CHAIRMAN. Thank you, Senator.

Senator Nickles.

Senator NICKLES. Thank you, Mr. Chairman.

I don't have a statement but just to congratulate you for having the hearing, and I am happy to be a cosponsor with you on your extension legislation.

The CHAIRMAN. Well, I am grateful for your cosponsorship and happy to have you here today.

Senator Dodd.

Senator DODD. I have no statement at this time.

The CHAIRMAN. Senator Grassley.

Senator GRASSLEY. Mr. Chairman, I wanted to come for two reasons; one, to ask to insert a statement in the record, an opening statement, but also I refer in this opening statement to the fact that this has been around since 1977. We don't have a whole lot of new information, but we have been extending for a period of time. I was in the House of Representatives when we first extended it, and I was involved in that extension, and I am a cosponsor of this one, and I intend to support its passage.

I also would like to make note of the fact and to welcome a professor from the University of Iowa, College of Medicine, the Department of Pediatrics and Biochemistry, on panel 3, Dr. Lewis Stegink, and make note of the fact that he is here and welcome him and in every way thank him for his taking time out of his busy schedule to come here to contribute to this knowledge on this issue.

The CHAIRMAN. Well, thank you, Senator.

Without objection, we will place your statement in the record as though delivered.

[Senator Grassley's opening statement follows:]

OPENING STATEMENT OF SENATOR GRASSLEY

Senator GRASSLEY. Thank you, Mr. Chairman. I am pleased to participate in this hearing on S. 484, the Saccharin Study and Labeling Act. This bill would extend the moratorium on the ban on saccharin for the fifth time since the Food and Drug Administration announced its intention to ban this sweetener in 1977. I am a cosponsor, and intend to support its passage.

Saccharin is used at the present time in many food and drink products. It is added to soft drinks, tabletop sweeteners, instant tea mixes, juices, breads, table syrups, candies, cake and frosting mixes, cookies, puddings, chewing gum, liquid diet meals, dessert toppings, and many others. It is also used in cosmetic products such as dentifrices, mouthwashes, lipsticks, and aftershave lotions.

Unfortunately, there is at the present time no complete substitute for saccharin. Aspartame cannot be used in most home baking or cooking, and cyclamates have not been approved by the FDA. I think it is clear that a ban on its use would seriously inconvenience consumers, particularly those who must diet to lose weight, and diabetics, and also people who make and market the many foods, drinks, and other products in which saccharin is now used.

It is also clear that we want to satisfy ourselves that there is no health hazard from use of saccharin. However, we also do not want to rush forward to ban this product on the basis of inconclusive evidence. We have had enough experience with hasty judgments, based on flimsy evidence, about products on which many people depend, both consumers and producers.

And, as you stated in your opening remarks, Mr. Chairman, the jury is still out on saccharin. No clear verdict emerges from the considerable research effort which has been directed to finding out whether this sweetener does indeed cause cancer in humans when used in amounts which might normally be consumed. It is appropriate, therefore, that we extend this moratorium until the Food and Drug Administration can demonstrate conclusively that this product causes cancer.

Thank you, Mr. Chairman. I look forward to hearing from our witnesses.

The CHAIRMAN. Senator Simon.

Senator SIMON. Thank you, Mr. Chairman.

I am basically here to learn, but let me just add—I recognize this is not the subject of the immediate consideration here, but I think at some point we ought to take a look at the Delaney amendment——

The CHAIRMAN. I am with you on that, Senator. [Laughter.]

Senator Simon [continuing]. And how we weigh the risks and benefits, that obviously we want to prevent harm to our population, but in the weighing of that, there are benefits and risks that have to be weighed. The Delaney amendment in its pure and present form does not permit the weighing of the risks and the benefits.

I have no further statement beyond that. I am here to listen and learn.

The Chairman. Well, thank you, Senator.

You raise a very good point. I, for one, am very happy to have you on this committee. I think you have added a lot since you have been here, and we look forward to working together with you on these very important issues.

I think these are important issues. The distinguished Senator from Ohio has raised some interesting points, and I think we have some excellent witnesses here today.

We will at this point receive for the record a statement by Senator Hawkins.

[Senator Hawkins' statement follows:]

STATEMENT OF SENATOR PAULA HAWKINS
ON S. 484

Mr. Chairman, I am sorry that my schedule did not permit me to attend today's hearings, because as you know, I am an original cosponsor of S.484, legislation to extend the period during which the Secretary of Health and Human Services may not take action to restrict the continued use of saccharin or products containing saccharin. It is unfortunate that year after year we are forced to once again expend valuable legislative time on enacting legislation which no member of Congress really opposes. We are forced into this ridiculous charade because of our own unwilingness or inability to reform our nation's archaic food safety laws.

I am not advocating an elimination of the Food and Drug Administration, or a reduction in their powers. They are needed and neccesary to protect the American consumer from harm. But this situation just points out how that agency's flexibility is restricted by statutes and how they are forced by statutory interpretation to carry out policies which they know are not in the public's best interests.

Since the proposed ban on saccharin in 1977, some 20 human studies have been undertaken and no overall association has been found between saccharin intake and bladder cancer. The National Cancer Institute conducted a study of 9,000 individuals and concluded that they saw "no evidence of increased riske with the long-term use of artificial sweetners in any other form or with use that began decades ago." Saccharin has been used for nearly a century by humans without proven adverse reactions. In fact, its benefical use, as the most versatile of the low-calorie sweetners, offers significant benefits to the growing number of Americans, now more than 68 million, who seek to reduce their caloric intake.

My preference would be to reform the Food Safety laws which prompted the original ban of a beneficial and irreplacable product based not on evidence from human clinical trials, but massive doses of saccharin in animals. However, until Congress agrees to address that issue, we are still faced with the task of legislatively restricting the Secretary's powers year by year. This Congress we have introduced legislation to extend the ban for three years. I hope my colleagues will recognize the wisdom and efficiency in this action and enact this legislation immediately.

By extending the authority for three years instead of one, we are not ignoring the legitimate issues regarding the safety of low-calorie food and beverage sweeteners. The fact that this hearing has been expanded to include a discussion of cyclamates and aspartame is evidence of our continued interest in the public's health and safety.

Mr. Chairman, I look forward to reviewing the testimony that is presented today.

The CHAIRMAN. We are going to begin with, I think, one of the great leaders in the Senate, Senator Alfonse D'Amato from New York, who has worked hard on this issue, who has tried to resolve it, and who, I think, has demonstrated and continues to demonstrate decided leadership in this area.

Senator D'Amato, we are happy to take your testimony first, and then we are going to move to the other witnesses.

Senator D'Amato.

STATEMENT OF HON. ALFONSE D'AMATO, A U.S. SENATOR FROM THE STATE OF NEW YORK

Senator D'AMATO. Thank you very much, Mr. Chairman, and let me thank you for inviting me to this hearing today on this important issue of substitute sweeteners as well as commend you, Mr. Chairman, for your sponsorship of this legislation.

I am delighted to join you as a cosponsor, and I think these hearings are most timely and useful, and as your committee undertakes these hearings today, you and the committee ought to be commended.

We must remember, however, that of the nearly 70 million people who use sugar substitutes, there are about 50 million who depend on saccharin. We should not delay or impede the access of saccharin to these people, a good portion of whom are diabetic.

Therefore, Mr. Chairman, the introduction of your legislation to extend for 3 years the moratorium on the ban of saccharin is basic and it is important. The main reasons for this extension, the fourth since the 1977 ban, are simple.

There is no evidence that the use of saccharin has an adverse effect on our Nation's health. Saccharin is one of our most tested food substances. Because of its 80 years of use without being linked to cancer, it has passed the all-important test of time.

Now, 20 human studies on saccharin support its safety. In fact, the absence of saccharin would be harmful to millions who should not use sugar to avoid medical problems associated with being diabetic or overweight. Test after test has shown that saccharin does not cause cancer in animals other than rats or at sites other than the bladder.

One study indicated that saccharin caused bladder tumors in rats when applied in 3-percent doses, and I think it is important that we undertake, what does that mean? Now, for humans, that would equal 750 cans of diet soda consumed on a daily basis for a lifetime.

The Chairman. I know some people who come pretty close. [Laughter.]

Senator D'AMATO. And so, Mr. Chairman, I am not aware of any epidemiological studies which show an association between saccharin intake and bladder cancer in humans. I understand that recent evidence indicates that it may have been the sodium in some of the experiments that caused the cancer in the laboratory rats.

Another reason to keep saccharin on the market is the lack of another complete sugar substitute. It is nice to say that we are developing these, but these substitutes that have been coming forth, Mr. Chairman, I think, raise unusual questions.

Although aspartame is used as a sugar substitute, its use is not as universal as saccharin's, and because of the sweetener's loss due to heat, aspartame, unlike saccharin, cannot be used in most cooking or baking. A gradual sweetening loss also occurs when aspartame is used in liquids. In fact, many diet soft drinks use aspartame and saccharin together.

So although the FDA supports its use, many scientists continue to fear the health effect of aspartame. And cyclamates, which are being reconsidered to be let back on the market, is not a complete sugar substitute, either, and its sweetener intensity is too low and, for many instances, would require its use in combination with other substitute sweeteners.

Although its effects are still suspect, some experts fear that there may be a chromosome breakdown and a cause of testicular atrophy. Even if the ban on cyclamates were reversed, the product could not be available until late this year, at the earliest.

The ideal low-calorie sweetener which could meet the growing consumer demand for a greater variety of reduced calorie products does not exist, Mr. Chairman. Saccharin, aspartame, nor any other sweetener is perfect on all accounts.

The answer for meeting this demand seems to be a multiplicity of sweeteners, each allowed to find its most effective role in the marketplace. The net result of a variety of sweeteners will be better tasting products that have adequate shelf life, extended safety margins, lower production costs for industry, as well as more product choices for the consumer.

The public outcry in 1977 when the FDA first decided to ban saccharin should not be forgotten. Its use was important to the public in 1977, and it continues to be an important use today.

Because the use of other sweeteners is limited, it is only reasonable to continue to allow saccharin on the market. Saccharin is the least expensive sugar substitute available.

Although I believe it is important to have hearings on this matter, it is equally important for millions of people dependent on saccharin that its availability is not disrupted. The current moratorium ends this month. We are perilously close to the beginning of the phaseout of this sweetener.

I support the continuation of studies on saccharin, but also, we must let the millions of Americans who depend on it for their restricted diets know that they will be able to continue to use it at least until the ban that you have proposed, the additional 3 years until May 1988, or until another all-purpose sugar substitute is found.

So I support quick action on S. 484, legislation to extend the moratorium on the ban of saccharin, and I thank you, Mr. Chairman, for giving me the opportunity of sharing these thoughts with you.

The CHAIRMAN. Thank you, Senator D'Amato. We appreciate your taking time out of what we know is a busy schedule to be here.

Senator D'AMATO. Thank you, Mr. Chairman.

The CHAIRMAN. Thanks so much.

I am pleased to welcome our various distinguished panels of witnesses to discuss these issues and to provide an overview of saccharin and other sweeteners from a scientific and regulatory perspective.

We will hear first from representatives of the Food and Drug Administration. We are happy to welcome Dr. Frank Young, the Commissioner of the U.S. Food and Drug Administration. Dr. Young, we are very pleased to have you here.

We will then hear from a panel of scientists knowledgeable about the current state of scientific data and analysis on saccharin. Third, we will hear from a panel on aspartame, which has become an alternative or a complement to saccharin in some applications.

Finally, we will hear from representatives of users of saccharin and other alternative sweeteners. This should be an interesting hearing.

Dr. Young, we are pleased to have you here. We welcome you to the committee, you and your associates, and we look forward to taking your testimony at this time.

STATEMENT OF FRANK YOUNG, M.D., PH.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DR. GARY FLAMM, ASSOCIATE DIRECTOR FOR TOXICOLOGY, CENTER FOR FOOD SAFETY, FDA; DR. SANFORD MILLER, DIRECTOR, CENTER FOR FOOD SAFETY, FDA; AND THOMAS SCARLETT, GENERAL COUNSEL, FDA

Mr. YOUNG. Thank you very much, Mr. Chairman. It is indeed a pleasure to be with you.

I would like to introduce my associates to you: Dr. Gary Flamm, on my far left, who is the associate director for toxicology in the Center of Food Safety and Applied Nutrition; Dr. Miller, who is the director of the center; and Mr. Scarlett, who is general counsel at FDA.

If I could, Mr. Chairman, in the interest of time, I would like to introduce my entire testimony for the record and read some of its highlights.

The CHAIRMAN. Without objection, we will put the entire testimony of all witnesses in the record. We would appreciate it if witnesses would summarize because then we will have more time for questions.

Dr. Young, your testimony will be inserted into the record at the conclusion of your oral presentation.

Mr. YOUNG. Thank you.

As you know, the FDA's proposal to ban saccharin was, to say the least, controversial. Saccharin had been widely used and popular for decades as an artificial sweetener and, in addition, as emphasized earlier, it had been perceived to be important in dietary management of persons attempting to control diabetes, obesity, heart disease, hypertension, and dental caries, to mention just a few issues.

Moreover, many question the reliability of using animal tests for banning saccharin in humans. Two generations of rats have been fed nearly the maximum of tolerated doses of saccharin for their entire lives, and it was argued that the bladder tumors seen in those studies might only occur at extreme dosage levels in laboratory animals and might bear no relationship, or a difficult relationship, to actual human experience.

Indeed, a cause-and-effect relationship between saccharin and human cancer had not been proven at the time of the initial moratorium. Although an epidemiological study by the Canadian counterpart of the U.S. National Cancer Institute had suggested an association between saccharin use and cancer in humans, the epidemiological studies in the United States were not completed.

Therefore, the moratorium stemmed from a combination of unanswered questions about the implication of the animal test results and the possibility that saccharin might have a substantial benefit for health, and that that needed to be weighed against the potential risks.

Thus, the action earlier of this and other committees was an effort to balance a number of competing considerations. Saccharin would remain on the market for the time being; additional studies would be done; and consumers would be warned so that they could decide for themselves whether or not to use saccharin in the face of scientific uncertainty about risk and benefit.

I would like to briefly summarize the action that FDA took. As a result of the moratorium, we endeavored to do the following things: First, we contracted with the National Academy of Sciences to review the existing data on saccharin.

Second, we conducted an epidemiological study with the National Cancer Institute to look for an association between saccharin usage and bladder cancer in humans and, in the process, resolve some of the apparent conflicts in the findings of the previous epidemiological studies.

Third, we decided to perform animal tests to learn whether saccharin causes cancer in a range of doses below the extreme high levels used in previous animal studies. These animal tests would also examine whether saccharin acted in animals as a direct carcinogen or as a promoter.

Basically, to explain the concept of a promoter, we have prepared a brief graph for you.

The initiator, in and of itself, on the far left, colored by green, can produce a tumor. And, as you can see, with more concentration or higher concentration of initiator, there is depicted an increase in tumor formation.

The initiator, as I said earlier, in and of itself, can produce a cancer. The promoter, when added in varying concentrations, does not produce a cancer, but the combination of an initiator and a promoter produces cancer. So it is the question of the relative action of saccharin as an initiator or a promoter that I am speaking to at this point, and thus FDA would examine this as well as look at the action of saccharin in human skin cells.

Senator METZENBAUM. Would you define the "promoter" term? I don't understand it.

Mr. YOUNG. I am sorry. A promoter is a substance which, by itself, will not produce a cancer, but when added with low concentrations of an initiator—an initiator defined as a substance by itself able to produce a cancer—the promoter would produce cancer when only low concentrations of initiator are present. OK?

Senator METZENBAUM. Thank you.

Mr. Young. Thank you. I appreciate your question and the opportunity to clarify that.

The studies with laboratory rats were conducted by the International Research and Development Corporation under the sponsorship of the Calorie Control Council. In addition, since the moratorium, over 170 other studies on saccharin in various areas of biological research have been published and are being reviewed, and we understand that this continues to be a field of active research, and, as was said in the introductory comments, there is no field of dietary research that is more carefully explored than the field of saccharin.

A number of studies investigating this very promotional activity of saccharin in the test animals have been published by various groups and are being carried out by FDA at the NCTR, and you will be hearing from Dr. Hart in a later panel about this. I will merely summarize, in a very terse form, the various studies.

The National Academy report concluded, among other things, that saccharin is a carcinogen of low potency in rats and a potential carcinogen in humans, but one of low potency compared with other carcinogens.

In the second stage of the report, the National Academy of Sciences recommended an overhaul of the entire food safety law so that FDA could have a range of options in regulating saccharin. I believe that was spoken to by you, Mr. Chairman, and other Senators earlier.

The NCI-FDA epidemiological study focused on the ability of saccharin to produce cancer in humans. There was an attempt, therefore, to determine whether a correlation exists between an artificial sweetener used and bladder cancer.

The study did not attempt to distinguish between saccharin and other artificial sweeteners such as cyclamate, although saccharin has historically been the major sweetener. The study is widely regarded as one of the best and most sensitive ever conducted.

This epidemiological study found no evidence in the aggregate of increased risk to long-term artificial sweetener uses or to those first exposed decades ago. The study concluded that artificial sweeteners, as they have been used in the United States in the past, did not have even a moderate carcinogenic effect on the human bladder.

Some increases in risk were seen, however, among individuals who were also heavy smokers, suggesting that saccharin might act as a promoter in that situation—as I mentioned earlier from this general slide—although the data were inconsistent and difficult to interpret.

As a general rule, it is an extremely difficult task for epidemiologists to study or detect "weak" human carcinogens, and the tentative findings in regard to heavy users were at least comparable to that of the National Academy of Sciences that saccharin is a potential carcinogen of low potency in humans.

The International Research and Development Corporation study with rats confirmed the carcinogenicity of saccharin in this species that was found in the premoratorium study.

Dr. Hart will deal in detail with the FDA's laboratory study, but I will only add a few comments. In rats and cultured human skin cells, our studies indicate that saccharin can act as a cancer promoter.

As a dose response analysis was also carried out, it was possible to determine that there was some degree of relationship to the dose under study. In mice, however, no effects were found in a fashion similar to that in rats.

On followup research that we are planning, we will focus on implications that these results may have for humans. It would also be helpful to know, for example, what the mechanism of saccharin is.

In 1977, we considered alternatives. To date, there is still not a single acceptable alternative to saccharin that can completely substitute for all of its use. Although aspartame is now approved for a variety of uses, it will not completely replace saccharin because it loses some of its sweetening effects at high temperatures such as baking.

The more direct relevance of aspartame use to saccharin moratorium is that the increased popularity of aspartame appears to be decreasing the use of saccharin, which we feel is a benefit. Thus, whatever the potential risks that existed in 1977 from the use of saccharin, they are essentially diminished as the general consumption of saccharin appears to go down.

Thus, we feel that it is no longer a risk that is any further than what we knew in 1977, and in fact, because of the decrease in the use of saccharin, in the epidemiological studies, we are somewhat less concerned. In addition, we are looking at other sweeteners, as you both have mentioned, and I am sure that there will be activity in the future.

In conclusion, therefore, as in the past, we still do not adequately know the answer to all of the questions and uncertainties giving rise to the original 1977 saccharin moratorium. The actual risk, if any, of saccharin to humans still appears to be slight, however.

Research to date has allayed many of our fears but has not totally resolved this central question with any degree of confidence. Moreover, while saccharin may pose some risks, its overall usage is decreasing, and the search for acceptable substitutes continues.

We therefore do not object to the extension of the moratorium, recognizing that at some point we must answer the issue definitely.

This concludes my statement, Mr. Chairman, and we would be happy to answer any questions that we could for you.

[The prepared statement of Dr. Young follows:]

STATEMENT

BY

FRANK E. YOUNG, M.D., Ph.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman:

I am pleased to have this opportunity to participate in the Committee's review of S. 484, which would extend the moratorium that expires next month on the banning of the artificial sweetener saccharin.

BACKGROUND

If enacted, S. 484 would extend for an additional three-year period the original saccharin moratorium that was enacted in 1977 and subsequently extended. That moratorium precludes any action by the Secretary of Health and Human Services to prohibit or restrict the sale or distribution of saccharin solely on the basis of studies made available to the Secretary as of the date of the moratorium's original enactment. The original moratorium legislation also provided that further research be conducted in an attempt to resolve existing scientific uncertainties, and that all products containing saccharin be labeled to warn consumers of its potential risks.

As you know, Congress enacted the moratorium in response to a proposed ban by the Food and Drug Administration (FDA) over use of saccharin in foods, beverages, and other products. FDA's proposal was precipitated by the results of a long-term animal study conducted by the Food and

Drug Directorate of the Government of Canada (1977) which showed that saccharin caused bladder tumors in laboratory rats. The Canadian study confirmed the results of two earlier chronic animal studies, one by the Wisconsin Alumni Research Foundation (1971) and one by FDA itself (1973). Moreover, the Canadian study resolved an uncertainty from the earlier studies by showing that the tumors were not caused by a particular impurity (orthotoluenesulfonamide) in saccharin that had been suspected of being responsible for the earlier findings.

FDA's proposal was, to say the least, controversial. Saccharin had been widely popular for decades as an artificial sweetener and, in addition, was perceived by many to be useful in the dietary management of persons attempting to control diabetes, obesity, heart disease, hypertension or dental caries. Moreover, many questioned the validity of relying on these animal tests as the basis for banning its use in humans. Two generations of rats had been fed nearly the maximum tolerated dosage of saccharin for their entire lives. It was argued that the bladder tumors seen in those studies might only occur at extreme dosage levels in laboratory animals and bear no relationship to actual human experience.

Indeed, a cause and effect relationship between saccharin and human cancer had not been proven. Although an epidemiological study by the Canadian counterpart of the U.S. National Cancer Institute suggested an association between saccharin use and cancer in humans, epidemiological studies in the United States were showing no such association.

The moratorium, therefore, stemmed from a combination of unanswered questions about the implications of these animal test results for humans, and the possibility that saccharin might have substantial health benefits that ought to be weighed against its potential risks.

In sum, the moratorium reflected an effort to balance a number of competing considerations: saccharin would remain on the market for the time being; additional study would be done; and consumers would be warned so that they could decide for themselves whether or not to use saccharin in the face of scientific uncertainty about risk and benefit.

RESEARCH EFFORTS

As a result of the moratorium, FDA endeavored to do a number of things: (1) contract with the National Academy of Sciences (NAS) to review existing data on saccharin; (2) conduct an epidemiological study with the National Cancer Institute (NCI) to look for an association between saccharin usage and bladder cancer in humans and, in the process, resolve some of the apparent conflicts in the findings of previous epidemiological studies; and (3) perform animal tests to learn whether saccharin causes cancer in a range of doses below the extremely high levels used in previous animal studies. These animal tests would also examine whether saccharin acts in animals as a direct carcinogen (cancer "initiator") or enhances the carcinogenic effects of other chemicals (cancer "promotor"). FDA would also conduct tests with saccharin on cultured human skin cells.

Studies with laboratory rats were also conducted by the International Research and Development Corporation (IRDC) under the sponsorship of the Calorie Control Council. In addition, over 170 other studies of saccharin in various areas of biological research have been published since the 1977 moratorium, and these are being reviewed. We understand various groups are continuing their research efforts in a further study of mechanisms of tumor action of saccharin. A number of studies investigating promotion activity of saccharin in test animals have been published by various groups in addition to those being carried out by FDA at the National Center for Toxicological Research (NCTR).

While I will summarize this research for you very briefly, including some human data, the main conclusion to be drawn is that the totality of the data that has become available since 1977 does not raise our level of concern over saccharin.

The NAS Report

The NAS report, which was transmitted to the Congress in two stages in 1978 and 1979, was a review of existing data and did not involve new studies. NAS concluded, among other things, that saccharin is a carcinogen of low potency in rats and a potential carcinogen in humans, but one of low potency in comparison with other carcinogens. In the second stage of the report, the NAS recommended an overhaul of the entire food safety law so that FDA could have a range of options in regulating saccharin.

The NCI-FDA Epidemiological Study

The Congress clearly indicated its concerns about the relevance of the animal findings and directed that appropriate efforts be made to determine whether saccharin induces bladder cancer in humans. An epidemiological study therefore was attempted to determine whether a correlation exists between artificial sweetener use and bladder cancer. The study did not attempt to distinguish between saccharin and other artificial sweeteners such as cyclamate, although saccharin has been historically the major artificial sweetener. The study is widely regarded as one of the best and most sensitive ever conducted.

The epidemiological study found no evidence in the aggregate of increased risk to long-term artificial sweetener users or to those first exposed decades ago. The study concluded that artificial sweeteners as they have been used in the United States in the past did not have even a moderate carcinogenic effect on the human bladder.

Some increases in risk were seen however, among individuals who were also heavy smokers, suggesting that saccharin may act as a promotor in that situation, and among the heaviest users of artificial sweeteners, although the data there were inconsistent and difficult to interpret. Although as a general rule it is extremely difficult for epidemiological studies to detect "weak" human carcinogens, the tentative finding with regard to heavy users was at least compatable with the NAS finding that saccharin is a potential carcinogen of low potency in humans.

The IRDC Study

This study with laboratory rats confirmed the carcinogenicity of saccharin in this species that had been found in the pre-moratorium study. It also found a direct correlation between the amount of the dose and the incidence of bladder tumors.

FDA's Laboratory Studies

I will only summarize briefly our activities in this area since Dr. Ronald Hart, the Director of our NCTR, will be testifying on them in detail later in this hearing.

In rats and cultured (in vitro) human skin cells, our studies indicate that saccharin can act as a cancer "promotor"; that is, it can enhance the effects of other carcinogens. A dose-response relationship was also seen. In mice, however, no such effects have been found, thus suggesting that saccharin can affect different kinds of animals quite differently.

The follow-on research that we are planning will focus on the implications that these results may have for humans. It would be helpful to know, for example, what saccharin's mechanism of action is in rats and in cultured human skin cells and whether these mechanisms operate in humans who consume saccharin. I can assure you that we will pursue every lead that presents itself to us in an effort to better understand how saccharin affects humans. Some studies are now being planned, while others inevitably will follow from clues as they arise, either serendipitously or otherwise.

ALTERNATIVES TO SACCHARIN

As in 1977, there still does not exist an acceptable alternative to saccharin that can completely substitute for it. Although aspartame is now approved for use in a great variety of products, it cannot yet be used to completely replace saccharin because it loses its sweetening effect when exposed to high temperatures, as in baking. The more direct relevance of aspartame use to the saccharin moratorium is that the increased popularity of aspartame appears to be decreasing the use of saccharin. Thus, whatever potential risks existed in 1977 from use of saccharin are diminished as general consumption of saccharin goes down.

Although new sugar substitutes are being developed, and food additive petitions have been submitted to FDA for some of them, approval is not imminent. In addition, while Abbott Laboratories has resubmitted its petition for approval of cyclamate, that petition is still under review.

CONCLUSION

In conclusion, today in 1985 we still have not adequately answered all of the questions and uncertainties giving rise to the original 1977 saccharin moratorium. The actual risk, if any, of saccharin to humans still appears to be slight, however. Research to date has allayed many of our fears but has not totally resolved this central question with any degree of confidence. Moreover, while saccharin may pose some risk, its overall usage is decreasing, and the search for acceptable substitutes continues. We therefore do not object to the extension of the moratorium, recognizing that at some point we must answer the issue definitively.

That concludes my testimony. I would be pleased to answer any questions.

The CHAIRMAN. Well, thank you, Dr. Young.

Senator Metzenbaum did raise questions on the side effects of cyclamates. We did not ask you to prepare remarks on cyclamates, but can we assume that you are aware of these concerns, and that any action you take on the issue will carefully scrutinize all the findings?

Mr. YOUNG. Absolutely. We will look first at the carcinogenicity issue and then examine other issues to be sure that we know the answers.

The CHAIRMAN. Well, so far saccharin has been found to produce no increased incidence of tumors in female rats, in hamsters, or even in guinea pigs. In mice, it appears to be a tumor inhibitor. Am I right on that?

Mr. YOUNG. Yes.

The CHAIRMAN. Now, how do these results impact on the extrapolation from saccharin's effect on male rats to its possible effect on human beings?

Mr. YOUNG. It is very difficult to extrapolate in any particular species to the effect on human beings, and it is certainly more comfortable if we know in more than one species that there is an effect of tumorigenicity.

We do have, in the case of male rats, this effect on bladder cancer, and we therefore can, by some degree of extrapolation, in the usual form of chronic toxicological studies, suggest that this might be a human carcinogen. But with weak carcinogens such as saccharin, this is very difficult, particularly when only one species is involved.

The CHAIRMAN. I see. It has been suggested that the quantity of aspartame in specific products should be included on the product label. Has FDA considered that suggestion?

Mr. YOUNG. We have not considered it in great detail, but we have explored it partially, and we feel, at least at this time, that from the safety that we know about the compounds, that we did not feel compelled to originally require that.

I could ask Dr. Miller to comment further if you would, sir.

The CHAIRMAN. Well, let me ask you this question before Dr. Miller does. Does FDA have adequate legal authority to require quantitative labeling if it concludes that such labeling is necessary?

Mr. SCARLETT. Yes; under section 409, the food additive amendments, we would be able to require that the quantity of aspartame be declared.

The CHAIRMAN. Dr. Miller?

Mr. MILLER. I was just going to comment that in the process by which food ingredients and food additives are approved, the assumption is that we have established the safety of it under the conditions of use to which it will be set, so the need for labeling, except in some isolated cases, generally is not required.

Nevertheless, there are circumstances when this may be necessary, and if it is believed by anybody that this is necessary, we would be glad to see the information and the reasons why and some idea of how to establish a label, and we would consider it, either in the form of a petition or a request.

But it takes some time to consider this, because if we go ahead and say we will have to put the amount of label, that then requires us to do appropriate compliance testing to be sure that that amount is not being exceeded.

The **Chairman**. I see. The approval of aspartame and its widespread use have, it seemed to me, obviously resulted in a reduction in saccharin consumption, and I suppose that the use of saccharin, especially as a table-top sweetener, reduces the use of aspartame.

Do you think it is better to have just one product, or is it better to have a multiple set of products being used?

Mr. **Young**. I feel very strongly that it is important to have multiple sweeteners for two reasons: First, by having multiple sweeteners, the overall load of an individual to a particular one, and any potential adverse reaction, is decreased.

Second, there appears to be an additive effect on the use of sweeteners. For example, if one called the standard amount of sweetener 100 units—and we will call one saccharin and the other aspartame—independently, each might use 100 units to get a particular desired effect.

If, however, one combined aspartame and saccharin, one might find 8 units of aspartame, 7 units of saccharin, for example, giving the same effect that 100 units of saccharin might alone, or 100 units of aspartame. That, therefore, would lower the total amount of the use of a sweetener at any particular time. So, it would be very beneficial to have multiple sweeteners.

The **Chairman**. What is the likelihood that in 1988, 3 years from now, there may be one or more additional sweeteners on the market? Specifically, what is FDA's timetable for a final decision on cyclamates and acesulfame K?

And assuming positive action on either or both, could the decision be challenged in administrative proceedings by an activist group or a competitor, and if so, how long would this ordinarily take?

Mr. **Young**. We feel that it is quite likely that by 1988 there will be one or more other artificial sweeteners on the market. It is difficult to project exactly, but let me give you the information as to where we are now.

With cyclamates, we expect in the not-too-distant future, within a few weeks to months, the report back from the National Academy of Sciences that will enable us to understand the potential risk of cyclamates.

As far as acesulfame K, we have just reviewed the data and have identified some additional information that appears to be required. We will be meeting with the sponsor within this next month. Once we get the information from the sponsor, we will be more able to determine what additional questions need to be resolved.

We feel that both of these will be under active review, and it is not unlikely that there will be action on either these or other sweeteners within the next 3 years.

The **Chairman**. Did the Food and Drug Administration consider the possibility of behavioral side effects with regard to the use and consumption of aspartame before its approval?

Mr. **Young**. Yes; we did, and I can provide more information directly for you from Dr. Flamm.

Mr. **Flamm**. The original petition which we had from Searle raised some questions concerning some neurological problems and brain lesioning, and that was the major issue, which was dealt with by our Public Board of Inquiry. They unanimously agreed that those neurological problems were satisfactorily dealt with by the data in the petition.

Subsequently, Dr. Wurtman of MIT raised additional neurological problems relating to behavior, and we have studied very closely his data and his hypotheses, and we have been in close contact with him ever since.

The CHAIRMAN. I see. Since its introduction, aspartame really has carved out a pretty big share of the artificial sweetener market, and certainly this question arises: Does the degree of current or projected aspartame consumption alter any of FDA's judgments that it is actually safe in the food supply?

Mr. YOUNG. Yes; we feel that, at our present level of knowledge, aspartame is safe in the food supply.

The CHAIRMAN. In particular, does the agency feel that predictable levels of aspartame consumption will elevate phenylalanine levels in the brain sufficiently to produce changes in behavior?

Mr. YOUNG. We have no evidence that aspartame at this time would produce increased levels of phenylalanine in the brain to modify its behavior.

The CHAIRMAN. I see. And you have checked that?

Mr. YOUNG. We have looked into this quite carefully. If I could, I would like to ask Dr. Flamm to provide further information for you.

The CHAIRMAN. All right.

Mr. FLAMM. There is a good deal of information both in animals and in humans which gives us a very high degree of comfort with current uses of aspartame. We do not feel that, given the current levels of use, there is a problem with phenylalanine except in those individuals who are known as PKU individuals, phenylketonurics, who lack the ability to metabolize phenylalanine and who suffer brain damage, dementia, from high levels of phenylalanine. That is why products containing phenylalanine bear a warning or a statement to PKU individuals.

The CHAIRMAN. So, we do have a warning for those particular people on aspartame products?

Mr. FLAMM. We do. That is correct. But beyond that, we do not feel that the evidence in humans or animals warrants concern for affecting either phenylalanine or the metabolites of phenylalanine, the neurotransmitters.

The CHAIRMAN. Well, do you feel that followup double-blind clinical studies to examine possible behavioral effects of aspartame are necessary?

Mr. FLAMM. Well, as a scientist, it is always good to get additional information, and I would be the last person on Earth to say don't do a study if it is going to provide us with further information.

But in direct answer to your question, we do not feel that there is a need to conduct those studies to show or to demonstrate that current levels of aspartame use are safe. We believe that has already been demonstrated.

The CHAIRMAN. Does phenylalanine occur naturally in foods?

Mr. FLAMM. Yes; it does.

The **Chairman**. How do the levels normally ingested compare with the amounts to be expected from consuming aspartame?

Mr. **Flamm**. Well, roughly speaking, a 12-ounce carbonated beverage sweetened with 100 percent aspartame—that is, no saccharin at all—would be equivalent to perhaps a third of a glass of milk.

The **Chairman**. I see. Let's turn to Senator Metzenbaum.

Senator **Metzenbaum**. Thank you.

Dr. Young, it is nice to see you here. I know you spent about 9 years of your life in my own community.

Mr. **Young**. Yes.

Senator **Metzenbaum**. I am happy to welcome you.

I have a question for you, or rather a statement, sort of, that really doesn't belong to you because I don't think you are responsible, but actually, it concerns me that the hearing was originally scheduled for March 19.

Three weeks ago, my staff was informed that your statement was nearly completed and was undergoing final review. Yesterday, we called for your statement and were told it was being reviewed by the OMB and that changes were necessary and that it would be ready by 5 o'clock. Then they were told there was disagreement about the conclusion and it wouldn't be ready until this morning.

Now, I have some difficulty with this because if it takes 3 weeks, what happens overnight? We have been testing these artificial sweeteners for 15 years. The question really comes about as to how long does it really take to pass the censors, and what do the censors have to add to this inquiry?

You are the chief public health officer in the country. How do you change your statement to fall in line with the OMB? What do they have to contribute to this issue?

I am wondering whether or not this committee might share your original draft to see, really, what you did think about, and then we will put your whole statement in the record. I don't care if we put the original draft in the record or not, but I would like to see the original draft.

Mr. **Young**. There was no major censorship, Senator. One of the issues that came forward was, as you, I was very concerned with being sure that there was the appropriate time for the moratorium, and therefore I spent a substantial amount of effort, personally and with my staff, looking at the time and coming to the conclusion that the 3-year extension was one that we would not object to.

But this was something that was brought to the staff's attention by me. I would certainly be pleased to share with you the earlier drafts if you would like.

Senator **Metzenbaum**. That would be excellent.

Now, as I understand, the question of whether it was 3 years or 2 years or 1 year was an in-house decision. Now, with whom do you meet at the OMB? Do they have scientists over there to advise you how to change your statements, or just people who are sharp-pencil users? Did David Stockman himself tell you what to say?

Mr. **Young**. No, sir. The bulk of the scientists related to nutrition reside in the Center for Food Safety and Applied Nutrition.

Senator **Metzenbaum**. Who are the people you meet with at OMB?

Mr. **Young**. Well, there are a wide variety of individuals at OMB that deal with FDA affairs. Bruce Artim is one. Mr. Ginsberg is another one, Doug Ginsberg. But, basically, I want to emphasize that the issue that we are talking about dealing with the delay, sir, of the testimony, was one that I initiated and reviewed again over the weekend and then met with my staff at FDA on Monday on.

Senator **Metzenbaum**. When did the OMB give clearance?

Mr. **Young**. Let me see. The OMB clearance was essentially completed this morning.

Senator **Metzenbaum**. This morning. When did you originally get it to them?

Mr. **Young**. The testimony was submitted a couple of weeks ago. I could give you the exact date. However, I don't carry this around on the top of my head, sir.

Senator **Metzenbaum**. And you will make available to us your original draft?

Mr. **Young**. Yes.

Senator **Metzenbaum**. You know, one of the reasons for concern is that the OMB, if I am not mistaken, didn't they sit on the FDA proposal to ban certain food colorings, red dye, et cetera, for—I guess permanently. Did you ever come out with that ban?

Mr. **Young**. The bulk of the discussion there in regard to the food additives was primarily administrative discussion within the Department and within FDA.

Senator **Metzenbaum**. Did you come out with it, finally?

Mr. **Young**. We have come out with another extension, a provisional list.

Senator **Metzenbaum**. Another extension, but no ban?

Mr. **Young**. That is correct.

Senator **Metzenbaum**. Wasn't OMB involved in pointing out to you the error of your ways or that there might be a value in reconsidering your decision?

Mr. **Young**. Actually, the administrative discussion was primarily within the Department, and we are still evaluating it within the Department of HHS.

Senator **Metzenbaum**. Now, in your statement, you say the totality of the data that has become available since 1977 does not raise our level of concern over saccharin. But in 1977, Commissioner, the FDA's level of concern over saccharin was sufficient for it to propose banning it from the market.

Now, are you saying that all the evidence since 1977 does not lower your concern, either, that the evidence justifies the 1977 FDA proposal to ban saccharin? Is there something that causes you to lower your concern?

Mr. **Young**. The basic concern that the FDA has is quite similar to that in 1977 with these two added points. First, the epidemiological study indicated that the level of expected risk that we had in 1977 was, when looked at epidemiologically, somewhat lower than we had expected earlier, and we derive a degree of comfort from that.

We also have not been able to find any additional species yet since 1977 that tumors occur in. Thus, although it is no question that the data that we had in 1977 and the data today are similar in regard to male rats, we do not have any increased incidence of tumor in other animals.

Therefore, we are close to the position that we were in 1977 with a somewhat diminished level of risk.

Senator **Metzenbaum**. Keeping in mind that in 1977 tests showed saccharin at 5 percent of the diet in the rat, let me quote to you from an internal FDA document from your own Cancer Assessment Committee dated August 1, 1984:

> The findings of the IRDC study support the following observations: One, the dose response for saccharin-induced bladder cancer has been shown to extend from 7½ percent to 1 percent saccharin in the diet of male Sprague Dawley rats.

So it has dropped from 5 percent to as low as 1 percent, according to a recent study. Doesn't that raise your concern?

Mr. **Young**. I believe—and I will ask Dr. Flamm to comment on this particular study in more detail—that the rate of tumors that you are talking about is a dose-response curve between 1 percent and 5 percent, and we have found then, as in the past, that there is an increased incidence of tumors at the high concentration only in relation to saccharin. As one drops down to low concentrations of saccharin, one does not see the same incidence of tumors, as I have tried to illustrate on the chart.

But perhaps I could ask Dr. Flamm to comment.

Senator **Metzenbaum**. This statement does not confirm what you are saying. This statement is a more general statement. Maybe Dr. Flamm ought to respond.

Mr. **Flamm**. Well, I think the one thing that has to be considered is that the earlier studies were done with only about 50 rats, with about 50 animals. The IRDC study used hundreds of animals. I believe they used about 700 animals in the group where they did find, in the 1-percent group, I believe it was five tumors, something of that sort, out of about 700 animals.

This is precisely what we would have predicted from the data that we had back in 1977. Now, whether that 1 percent response represents a true reproducible response or not, we do not know, because it is not all that dramatically different from what you would have expected from control animals that were untreated, because the background incidence is not terribly far from that level.

But whether that is the case or not, I think the important fact is that it does not raise our concern over what we had in 1977 for the simple reason that if somebody had asked the question, Would you be able to find bladder cancer if you had 700 animals in a group? We would have said yes, we presume that that would be the case.

Senator **Metzenbaum**. Let me ask you this. If you had 700 animals and they were not fed saccharin, would you expect to find 5 cases of cancer in that 700 animals?

Mr. **Flamm**. I would expect to find, I believe, around two, two to three. So finding five is certainly not remarkable. When I look at historical control data, going from groups of 50 to 100 animals each, I find that sometimes the incidence goes up as high as 3 or 4 percent.

Senator **Metzenbaum**. Well, 7½ percent of 700 is something around 52, I would guess. How many would you expect to find if the same animals were not fed saccharin?

Mr. **Flamm**. Well, in a group of 700, I would expect to find maybe two or three bladder tumors in Sprague Dawley male rats.

Senator **Metzenbaum**. So you would find 2 or 3 out of 700, and you would expect that much cancer in a group of rats under any and all circumstances?

Mr. **Flamm**. That is right.

Senator **Metzenbaum**. And it goes up to as high as 50. When you say that the incidence can run anywhere from 1 percent to 7½ percent, what does that mean?

Mr. **Flamm**. No, I was talking—the 1 percent to 7½ percent is the level of saccharin in the diet.

Senator **Metzenbaum**. Oh, all right.

Mr. **Flamm**. The control incidence or the background incidence is around one-half of 1 percent.

Senator **Metzenbaum**. How many rats were in the whole study?

Mr. **Flamm**. Well, it was what they call an unbalanced design; that is to say, they had many more animals at the low dose than they had at the——

Senator **Metzenbaum**. At the what?

Mr. **Flamm**. They had more animals at the low dose, at the 1 percent dose, than they had at the 7½ percent. There were thousands of animals in the entire study, but I don't know the exact number.

Senator **Metzenbaum**. So as you fed more saccharin to the rats, there was a correlation, and there was a higher incidence of cancer?

Mr. **Flamm**. That is correct.

Senator **Metzenbaum**. I think we are going to get to that study on panel two, so I will hold my further questions.

In 1977, the FDA estimated that saccharin could cause up to 1,200 additional cases of bladder cancer a year, assuming everyone in the United States consumed the saccharin equivalent of one diet soda a day.

Do you still stand by that estimate, Dr. Young?

Mr. **Young**. We still stand by the concept that the results that we have today are quite similar to those that we had in 1977, with the exception of a somewhat lower incidence, but those numbers, by whatever the parameters were, are quite similar to where we would come out today.

But again, I would ask Dr. Miller for a detailed analysis of that, if you would. Dr. Miller?

Senator **Metzenbaum**. In answering, Dr. Miller, would you be good enough to tell me how many cases of bladder cancer you would expect to find on an annual basis in this country?

Mr. **Miller**. Well, I am going to defer again to Dr. Flamm because he has followed that study. The study that we are talking about——

Senator **Metzenbaum**. It is pretty smart the way you fellows throw all these to Dr. Flamm. [Laughter.]

Mr. **Miller**. Well, everybody has to have their experts. The study that we are talking about is a study that was done at the request of the Congress when the first moratorium bill was passed, and it involved probably the largest retrospective epidemiological study done, and maybe one of the best ones.

It was designed specifically to try to test this question of whether or not the risks which were estimated by the assessments done at the time were in fact taking place in society, or was it greater than we had estimated, or was it less than we estimated?

And so NCI and FDA then performed this very large retrospective epidemiological study, and I would like to ask Dr. Flamm to comment on that.

Mr. **Flamm**. Well, in direct answer to your question about the incidence of bladder cancer in the United States, it is higher among males than females, and there is a lifetime expectation in U.S. males of about 1.5 percent of developing bladder cancer.

Senator **Metzenbaum**. Well, the question I have is that FDA at that time estimated that up to 1,200 additional cases of bladder cancer a year could be caused by the ingestion of the saccharin equivalent of one diet soda a day.

Now I am asking you, how many cases of bladder cancer are discovered annually? I am trying to relate the 1,200 to whether that is as compared to 12,000 or whatever.

Mr. **Flamm**. Well, I could calculate it for you, Senator. Off the top of my head, I think it is around 30,000 cases. I believe that is correct.

But in reference to the risk estimates that were done by FDA, unless I am mistaken, subsequent to our estimate, there was the National Academy report as mandated by the Saccharin Study and Labeling Act of 1977, and they undertook risk assessments and showed—which was not terribly surprising— that depending upon the assumptions that you make, the risk ranges enormously from a very, very low risk of about one in 30 million or so up to much, much higher risk, closing in on something like 1 in 1,000 or 1 in 10,000.

So there is a huge range that was dependent very much upon the scientific assumptions made and the models selected. I think what is really at issue here is really the mechanism by which saccharin causes cancer in rats and what the implications are to humans.

I think our state of ignorance is somewhat similar to what it was in 1977 relative to what the implications truly are. But the one thing that we have managed to do is to show through these epidemiologic studies that you have heard about that saccharin consumption clearly has not been a significant risk factor in bladder cancer among people living in the United States.

Senator **Metzenbaum**. Tell me again what those epidemiological studies, how you arrive at that conclusion.

Mr. **Flamm**. These were case-controlled retrospective studies that were carried out by epidemiologists at the National Cancer Institute utilizing their so-called SEER Program, which is S-E-E-R, standing for Surveillance Epidemiology and End Results Program, and they were able to look at tens of thousands of bladder cancer patients and able to deduce retrospectively what their saccharin consumption was, and concluded that there was no evidence, with the one exception that had been noted, associating bladder cancer with saccharin consumption.

Senator **Metzenbaum**. Well, isn't it a fact that you wouldn't discover the cancer for quite a long lag period after the saccharin was ingested?

Reading from the Federal Register of April 15, 1977:

> As discussed previously, cancer has a long latent period, requiring 15 to 30 years before it can be detected. Although saccharin has been used in food for over 70 years, it is only in the past 15 to 20 years that its use has become substantial.
>
> Thus, it is probably too early to ascertain from human epidemiological studies the number of bladder cancers associated with saccharin consumption. The estimated increase from this moderate use of saccharin cannot be detected in human epidemiological studies. Such studies usually can only detect increased risk of 200 to 300 percent, in other words, two to three times the baseline rate or greater.

Now, is it not the fact that you would have difficulty in making a detection of the impact of the use of saccharin by a short-lived exposure, short-lived period of time, and you would have to wait a number of years in order to see whether indeed it is causing cancer, and may very well be doing that at this moment?

Mr. **Flamm**. Well, I am telling you what the view is of the group of internationally recognized epidemiologists who have taken into account the caveats that you just mentioned. Their view is, combining the NCI study with a more recent Danish study which attempted to go back and very carefully assess saccharin exposure virtually from the birth of the individual, that the totality of the evidence makes clear that saccharin is not a major risk factor in bladder cancer in the United States or those parts of the world where these kinds of studies have been conducted.

Senator **Metzenbaum**. Well, I might say that the statement I read previously from the Federal Register was an FDA statement.

Mr. **Flamm**. I don't dispute the statement at all, Senator. I think it is a correct statement.

Senator **Metzenbaum**. Now, there was an industry-sponsored study on saccharin which confirmed the position that FDA took in 1977 when it proposed the ban. Robert Shuplein, Deputy Director of FDA's Office of Toxicological Sciences, said that that industry-sponsored study was the best study that has ever been done on saccharin. The important point is that it verifies and extends the Canadian study.

On the second study, he says, "The fact that saccharin has a promotional effect at a lower level is of some concern." That had to do with the point you made about the promotional impact of it.

Under those circumstances, it seems to me that in 1977 there was enough evidence for you to ban it. Yet Congress came along and provided a lag period. Now there are more studies. These studies confirm and reaffirm the earlier findings. The earlier findings indicated that if everybody drank 1 bottle of diet pop a day, that it could increase the number of cancers in this country 1,200 cases a year. You are here saying that that doesn't worry you, that that is not a matter of great concern, and I am having difficulty—have there been any clinical studies made with respect to the use of saccharin and the impact upon the human body?

Mr. **Young**. If I could, let me return to your earlier question, and I will submit for the record this article in Lancet in 1980, but I would like to summarize one clinical study for you.

In this case, 3,010 patients with cancer of the urinary bladder and 5,783 controls drawn from the general population of ten geographic areas of the United States were interviewed. Subjects who reported ever having used artificial sweeteners or artificially sweetened foods or beverages showed no elevation in risk.

However, positive associations between various measures of use of artificial sweeteners and risk of bladder cancer were seen in several subgroups, and these were the subgroups with very high concentration or perhaps other initiators.

Senator **Metzenbaum**. Would you repeat that? You said that there were 3,000 who had bladder cancer.

Mr. **Young**. That is correct. This is epidemiological study by NCI and FDA.

Senator **Metzenbaum**. Five thousand and——

Mr. **Young**. There were 5,783 controls. They matched the age and sex of these and looked at the controlled study. In this summary, they concluded that the subjects, whoever had used sweeteners or artificial sweeteners in foods and beverages showed no elevation of risk. In other words, if you looked at the total population, there was no elevation in risk.

There were two subpopulations that were somewhat of concern, and those were first with possibly other factors such as smoking, and second, with very high use. They went on to say that inconsistencies in the data suggested that the positive associations may be due to chance, but it is noteworthy that the subgroups were those chosen a priori to test hypotheses derived from laboratory experiments.

So, basically, the epidemiological study does provide some degree of comfort that the general population may not have a substantial risk from saccharin but does provide some question as to whether the other subgroups were either from chance or whether it was significant, and I would submit this for the record, sir.

Senator **Metzenbaum**. Well, as I understand it, where there were smokers, those who were using sweeteners, that was one of the control groups, as I understand it.

Mr. **Young**. Sweetener plus smoking was one of the experimental groups, yes.

Senator **Metzenbaum**. And were the number of cancers in that group 60 percent higher for those who were using sweeteners?

Mr. **Young**. That is correct. There was a higher level in that group.

Senator **Metzenbaum**. Was it 60 percent?

Mr. **Young**. I believe so.

Senator **Metzenbaum**. All right.

Mr. **Young**. Gary, do you remember that exactly?

Mr. **Flamm**. I don't remember the exact figures.

Mr. **Young**. We will submit that for the record.

Senator **Metzenbaum**. And what was the other variation in the other subcontrol group?

Mr. **Young**. The other subcontrol group was the high usage, and we will submit that number for the record as well.

[The material referred to follows:]

HEW NEWS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

P79-40
FOR IMMEDIATE RELEASE
December 20, 1979

WAYNE PINES (FDA)--(301) 443-4177
PAT NEWMAN (NCI)--(301) 496-6641

The National Cancer Institute (NCI) and the Food and Drug Administration (FDA) today released the preliminary findings of a $1.5 million epidemiological study that examined the relationship between the use of artificial sweeteners such as saccharin and cyclamate and the incidence of bladder cancer in humans.

The preliminary results of the study conducted by NCI were that there was no increased risk of bladder cancer among users of artificial sweeteners in the overall study population. However, there was some evidence that sweeteners may be hazardous. That evidence came from observations of three groups:

1. Heavy users of artificial sweeteners, particularly those who consumed both diet beverages and sugar substitutes, showed a 60 percent increased risk of bladder cancer. Heavy use was defined as six or more servings a day of a sugar substitute or two or more eight-ounce diet beverages a day.

2. People who smoked cigarettes heavily and who also made heavy use of artificial sweeteners showed a higher risk of bladder cancer than heavy smokers who did not use artificial sweeteners. The investigators have not yet defined the specific magnitude of that increased risk. Heavy cigarette smoking was defined as more than two packs a day for men and

more than one pack a day for women.

3. Those women who normally would be at low risk for bladder cancer, but who consumed sugar substitutes or diet beverages twice or more a day, had a 60 percent greater risk of bladder cancer compared with similar women who never used artificial sweeteners. The risk increased with the amount of artificial sweeteners used. Based on these data, the authors estimated that low-risk women who never used artificial sweeteners had an estimated yearly rate of about five cases of bladder cancer per 100,000, while similar women who consumed sugar substitutes or diet beverages twice a day or more had an estimated yearly rate of an additional three cases per 100,000.

The authors of the study concluded that while saccharin and cyclamate are not strong carcinogens, they should be regarded as potential risk factors for human bladder cancer, based on the results of this study plus previous experiments in laboratory animals.

The authors also said that saccharin and cyclamate may enhance the cancer-causing effects of heavy cigarette smoking.

They said the findings of this study appear consistent with the results of animal studies that concluded that saccharin was a weak animal carcinogen when given alone and also was able to enhance the carcinogen action of other chemicals.

One purpose of the study was to examine the conclusions of previous, smaller studies that found a 60 percent increased risk of bladder cancer among men who consume sugar substitutes. The NCI study did not confirm the 60 percent rate. The investigators said the increased risk of bladder cancer to males in the NCI study, from average use of sugar substitutes, would not exceed 18 percent.

The authors cautioned that further analysis of the preliminary data will be needed to separate with precision the effects of saccharin and cyclamate. Cyclamate was the predominant artificial sweetener used during the 1960's; after FDA banned its use in 1970, saccharin became the only artificial sweetener available in the United States. The authors also noted that the study could not assess the effects of consuming artificial sweeteners during pregnancy or in early childhood.

The NCI study, conducted under an interagency agreement with FDA, was prompted by the Saccharin Study and Labeling Act of 1977, in which Congress temporarily prohibited FDA from restricting the use of saccharin in diet sodas and other diet foods, but ordered further study of the popular artificial sweetener. Congress' action stemmed from an FDA announcement that it intended to restrict use of saccharin in foods and permit its continued use only as a table top sugar substitute, provided there was evidence that it benefited some people such as diabetics or people on weight control diets.

FDA's proposed restrictions were based on three studies, two conducted in the United States and one in Canada, that demonstrated that saccharin could cause cancer in test animals at high doses.

In a statement on saccharin issued today, Dr. Jere E. Goyan, Commissioner of Food and Drugs, said:

"This was a complex study and further evaluation of the data is required. NCI's evaluation thus far, however, indicates that this study is consistent with previous animal studies which concluded: that saccharin is a weak carcinogen. This is the conclusion that scientists from FDA, the National Academy of Sciences and the Congressional Office of Technology Assessment previously had reached. FDA will evaluate these new NCI data and gauge their significance."

Dr. Goyan concluded: "I reiterate my concern about the consumption by so many Americans, especially young people, of large amounts of saccharin. More than half the subjects in this study were 67 years old or older, and therefore consumed much less artificial sweeteners than their children and grandchildren are today. We may have to wait 20 or 30 years to assess the possible effects on our young people of consuming large amounts of a weak carcinogen."

NCI's study, the largest of its type ever conducted, comprised interviews from March, 1978, to June, 1979, with more than 3,000 bladder cancer patients and almost 6,000 people from the general population who did not have cancer, but who were similar in age and sex. Three of every four persons in the study were men.

Bladder cancer is three times more common in men than in women, and is more common among cigarette smokers and among workers exposed to certain chemicals on the job.

The study was conducted in five states (Connecticut, Iowa, New Jersey, New Mexico and Utah) and five metropolitan areas (Atlanta, Detroit, New

Orleans, San Francisco and Seattle). The authors of the study were led by Dr. Robert N. Hoover and Ms. Patricia H. Strasser of the Environmental Epidemiology Branch at NCI.

Bladder cancer, diagnosed in 15 out of every 100,000 persons, is the sixth most common form of cancer in the United States. The disease usually occurs in older age groups, and more often in whites than in blacks, Orientals, or American Indians.

####

Collaborating authors of The National Bladder Cancer Study were: Robert N. Hoover, MD, DSc., principal investigator; Patricia Hartge Strasser, MA, MSc., study coordinator; Dr. Margaret Child, Atlanta Cancer Surveillance Center; Dr. Donald Austin, California State Department of Health; Dr. Kenneth Cantor, Environmental Protection Agency; Dr. David Thomas, Fred Hutchinson Cancer Research Center; Dr. J. W. Sullivan, Louisiana State University Medical Center; Dr. Marie W. Swanson, Michigan Cancer Foundation; Dr. Thomas J. Mason, Dr. Max Myers, Ms. Debra Silverman, National Cancer Institute; Dr. Ronald Altman, Ms. Annette Stemhagen, New Jersey State Department of Health; Dr. Ambati Narayana, Dr. David Culp, University of Iowa; Dr. Charles Key, Mr. Daniel Kutvirt, University of New Mexico; Dr. Dee West, Dr. Joseph Lyon, University of Utah.

Single copies of the "Progress Report to the Food and Drug Administration From The National Cancer Institute Concerning The National Bladder Cancer Study" are available from the NCI Office of Cancer Communications, Bldg. 31/10A21, Bethesda, Maryland 20205.

Senator METZENBAUM. And what was the increased number of cases in the other group?

Mr. YOUNG. The increase above background in that one was approximately—as a figure normalized to the control of 1, this was 1.45, or almost about 0.5 higher than the——

Senator METZENBAUM. About half again as much?

Mr. YOUNG. Half again as much.

Senator METZENBAUM. All right.

Mr. YOUNG. Above background.

Senator METZENBAUM. Pardon?

Mr. YOUNG. Above the background number, as was mentioned by Dr. Flamm.

Senator METZENBAUM. I have additional questions, but my distinguished colleague has to get away. I guess the bell didn't go off, and so I just kept going on.

I yield to Senator Simon with the understanding that I have additional questions.

Senator SIMON. Yes, and I will just really have one or two brief questions.

In all the maze of language that I hear here, what I am looking for is something more precise that I have to deal with, and that is whether we have a moratorium or whether we don't, and whether it is wise.

You say you do not object to a 3-year moratorium. Let me ask you this, Commissioner. You may want to refer it on down the line. Dr. Flamm seems to get all these questions eventually down there. [Laughter.]

If you were a member of the U.S. Senate and you had to vote, on the basis of the knowledge that you have, on a 1-year moratorium, 2-year moratorium, or a 3-year moratorium, what would you vote for?

Mr. YOUNG. There is a great dilemma here because we are basically revisiting 1977. The 1977 moratorium was put into place because there were controversies and a balance between public demand for a product and the potential hazards of the product.

Under those circumstances, it was deemed prudent to have a moratorium while we developed more information, but to clearly label the product as potentially hazardous to one's health and let the individual make a choice.

Our recommendation is that we do not object to the continuation of that process.

Senator SIMON. I understand, but you have not answered my question. [Laughter.]

If you had to vote, as a member of this committee, for a 1-year moratorium, 2-year moratorium, or a 3-year moratorium, what would you vote for?

Senator METZENBAUM. He would take the fifth.

Mr. YOUNG. No, I am trying to answer your answer as clearly as I could. I would at this point——

Senator SIMON. I have the impression you are trying to answer it as not clearly as you can. [Laughter.]

Mr. YOUNG. I would vote for the 3-year moratorium at this point.

Senator SIMON. All right. I thank you. I thank my colleague for yielding.

The **Chairman**. How much longer will you be, Senator Metzenbaum, because I can only go until 4 today. We will have to recess until later.

Senator **Metzenbaum**. I would guess I would be another 10, 12, 15 minutes.

The **Chairman**. If we go much longer, we won't get to even the second panel.

Senator **Metzenbaum**. Well, I will try to move along.

The **Chairman**. All right. And I don't want to cut you off, naturally.

Senator **Metzenbaum**. I appreciate that, Mr. Chairman.

The **Chairman**. I have been yelled at before by Senator Metzenbaum when he was cut off.

Senator **Metzenbaum**. No, I have been very nice to you today. [Laughter.]

The **Chairman**. Yes; he is just great. He is patting the chairman here. [Laughter.]

Senator **Metzenbaum**. That is right.

I want to come back to the issue of labeling, but I will do that rather briefly. But I would like to ask you, on the NutraSweet question, Common Cause published an investigation last year that was very critical of the way the FDA approved NutraSweet.

One of the major issues was the quality of Searle's testing for that product. Now, let me read to you from an FDA document dated January 10, 1977. It is a letter from Richard Merrill, chief counsel for the FDA, to the U.S. attorney in Chicago:

> We request that your office convene a grand jury investigation into apparent violations of the Food and Drug Act by G. D. Searle for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the drug aldecon and the food additive aspartame * * *

Meaning NutraSweet.

Now, Mr. Young, these irregularities in animal tests were discovered by a special task force investigation which brought into question Searle's testing practices from 1966 to 1977. Common Cause says the FDA relied on these tests to approve NutraSweet, tests which were so bad that the FDA general counsel recommended that Searle be brought before a grand jury for the way they were conducted.

May I have your response as to this whole issue, because I think it relates to the saccharin issue, because if we don't extend the law and we force all people into NutraSweet, then I think we have to be concerned about its safety as well, and so there is somewhat the horns of a dilemma that we in the Congress are placed upon, and I would like to get your feeling on this issue.

Mr. **Young**. Senator, in general, it is very important that all tests be done accurately and appropriately; otherwise, the American people cannot have any confidence in such testing.

I would like to ask Mr. Scarlett whether he has any direct information on this particular allegation. It antedated my coming into the commissionership.

Mr. **Scarlett**. Some of the Searle-sponsored studies on aspartame were poorly conducted. There were many studies of aspartame. FDA's decision to approve aspartame was based on many more studies than those few studies on aspartame that were involved in the referral from which you were quoting that my predecessor, Richard Merrill, wrote to the U.S. attorney.

In addition, two tasks groups, one outside the FDA and one inside the FDA, went back and they looked at those studies, and they verified to the degree that they could that the studies were in fact authentic.

They did not establish that the studies were flawless. Many animals studies have flaws. These had flaws. That was all taken into account in the overall decision that there was enough scientific basis to approve aspartame, including many studies that were not involved in that particular incident to which you refer.

Senator METZENBAUM. Was the Bresler report one of the reports you are talking about that was done subsequently? And was one the UAREP report?

Mr. SCARLETT. Yes. The Bresler report is the FDA task group, and the UAREP report is the outside task group.

Senator METZENBAUM. Didn't both of those panels raise additional questions as well with respect to the safety of the use of aspartame?

Mr. SCARLETT. Not that I know of.

Senator METZENBAUM. I think, if you check, you will find that they did. I might say the grand jury investigation, as I understand it, was dropped because they said you cannot indict on the basis of sloppy testing or failure to make adequate testing. Is that your understanding as to why it was dropped?

Mr. SCARLETT. There were some questions concerning the interpretation of our testing regulations.

Senator METZENBAUM. Dr. Young, let me ask you, did the FDA ever require any followup tests with respect to the safety of NutraSweet?

Mr. YOUNG. The FDA looked at some of the complaints that came in in the early days of approval of NutraSweet. These were analyzed in depth by the CDC based on the review of consumer complaints. They were not a prospective epidemiological study but the analysis of consumer concerns.

Based on that consumer concern analysis, we did not find evidence that would indicate a major or substantial or even minor problem with aspartame, with the exception of a subgroup in the population, younger females, and that is under further study at this point.

Senator METZENBAUM. Dr. Bresler, who was head of the task force, was quoted on the key cancer brain test, which he reviewed, as saying—and he didn't say it to me, but Common Cause quotes him as saying—"It was a lousy study, it was a sloppy study. You don't have to be brilliant to know that."

They also quote Dr. Endicott, the head of the Pathologist Review Committee, which was the UAREP, saying, "The panel's conclusions did not mean the tests were valid."

In view of these—here is your task force that has checked it out, here is your pathologists that have checked it out, and they seem to have continued concern, and yet I gather you have no ongoing tests going on except those with respect to young girls. Is that what you said?

Mr. YOUNG. This report that you refer to is different than the consumer information that I cited. I would like to ask Dr. Flamm to respond directly to that report.

Mr. FLAMM. We feel that we have an adequate amount of animal carcinogenicity data for aspartame. It is correct that there were questions raised over how Searle conducted their studies, how they assured that they had adequate documentation for what they had done, and it is certainly true that this gave rise to our good laboratory practice regulation, which has been a very useful regulation to us in terms of assuring the validity and authenticity of animal data submitted to us in support of a petition.

There were, as Mr. Scarlett indicated, more than just the minimum number of studies necessary to support a petition of this kind. There were multiple studies. The final one which they did in accordance with our protocols, the two-generation study, was in fact, according to the side-by-side comparisons of diagnoses made by their pathologists versus UAREP pathologists, very, very well performed, and we felt that it was a fully adequate study on which to base our decisions.

Now, we did look at the data upside down, inside out, and backward, and we ourselves called attention to specific concerns which were subsequently resolved, and it may be some of that that you are referring to.

Senator METZENBAUM. Dr. Flamm, the FDA convened a scientific board of inquiry on NutraSweet in 1980. That board recommended that NutraSweet not be approved until further tests could be run on whether NutraSweet caused brain tumors. But Commissioner Hays overruled his Scientific Board of Inquiry and approved aspartame for use in dry foods in April 1981. Why?

Mr. FLAMM. Commissioner Hays referred the conclusions of the board back to the Bureau of Foods, which is now the Center for Food Safety and Applied Nutrition, and the scientists within the Bureau of Foods and their Cancer Assessment Committee reviewed the decision, rereviewed the data, and put together what in essence was a rebuttal to the proposal that aspartame be tested yet one more time for carcinogenicity.

Commissioner Hays then had that rebuttal reviewed by his team of scientists who in essence recommended that the recommendations of the Bureau of Foods be accepted, and he acted based on those recommendations.

Senator METZENBAUM. Didn't three of the six scientists on the advisory panel advise him that the key Searle tests could not be relied upon—it was a commissioner's panel— and suggested that the aspartame be rejected for approval? Am I not correct in that? Three out of six members of the commissioner's panel of outside experts advised him that his final decision should be not to approve, and then he then goes ahead and approves. Isn't there cause for worry? This was after the board of inquiry.

Mr. FLAMM. All right.

Mr. SCARLETT. Could I ask for a clarification? Excuse me, Gary. There was no outside board advising the commissioner. I don't know which six people you are referring to. They may have been advisors internally.

Senator METZENBAUM. Well, I am reading from an in-house memo of the Department of Health and Human Services dated May 19, 1981, from Robert J. Condon; subject: Aspartame, dissenting opinion of brain tumor issue," to Joseph A. Levitt: "I do not concur that aspartame has been shown to be safe with respect to the induction of brain tumors. My opinion is based on the following reasons."

Mr. SCARLETT. Yes, I know who Dr. Condon is. Those were internal advisors to the commissioner. There was some disagreement, but the commissioner——

Senator METZENBAUM. Pardon?

Mr. SCARLETT. There was some disagreement, but the commissioner ultimately decided that the evidence weighed in favor of approving the product, and the chairman of the board of inquiry with which the commissioner was in disagreement eventually wrote to him and publicly endorsed his decision.

Senator METZENBAUM. What I am saying to you is that three of the six dissented. Is that correct?

Mr. SCARLETT. That is correct.

Mr. MILLER. Can I make a point, Senator? When the Center's comments concerning the PBI's decision was sent to the members of the committee, there is a letter in the file which I think you have from the chairman of the committee saying that he was convinced that we had answered his concerns in that regard.

In addition, in an article in Science, both he and another member of the committee were asked what their opinion was after reading this, and two of the three members said that they were convinced by these arguments and had no further concerns, and the third member didn't comment at all.

Senator METZENBAUM. Didn't the letter also cite a Japanese study?

Mr. MILLER. That is right. He cited a study which had been just reported from Japan, yes.

Senator METZENBAUM. That what?

Mr. MILLER. A Japanese study, yes.

Senator METZENBAUM. The Common Cause quotes MIT's Dr. Wally Notta, head of the 1980 scientific board of inquiry, as saying that he was surprised the FDA approved NutraSweet for soft drinks, "that it never figured in our decisionmaking." He said he definitely would have wanted to look more closely at other tests if he had known NutraSweet would be so widely consumed in soft drinks.

I guess what is concerning me is, I think we have a situation where NutraSweet was approved, as I recollect, for dry substances. Nobody anticipated that it would be used to the extent it is being used at the present time in the diet drinks, which is in far greater quantities, far greater concentration.

There are no studies on that. There is no scientific evidence on that, as I understand it. It still seems that when three out of six dissent from the conclusion when the commission or the board, whatever its name may be, comes to one conclusion and then Dr. Hays overrules them, what bothers me about all of this is, can the American people rely upon the FDA, or is the FDA in some way going along with the tide, checking out what they should say over here with the OMB?

I sort of wonder what they did say over there. I am wondering whether they were concerned about an administration position on cyclamates and NutraSweet and saccharin.

We have before us only one issue. Do we renew or provide for another extension of the ban on the use of saccharin? I guess I would ask you, Commissioner Young, you answered Senator Simon, if you were forced to vote, as a Member of the Senate, you would vote for the 3 years. I guess you would vote for the 2 years, too, if you were asked and could vote for the 3. Is that probably correct? Or 18 months, if you were asked?

Mr. YOUNG. Yes.

Senator METZENBAUM. Would you vote for 4 years?

Mr. YOUNG. I think the issue needs to be brought, as I said, to a resolution. The Congress had intervened earlier in 1977 to develop a position in which the FDA had moved toward bringing forward a ban, and the Congress said stop. It said stop for some reasons that balanced public interest against a labeling to deal with the compound as a potential carcinogen.

Studies to that time have confirmed where we were in 1977, somewhat decrease the risk from the epidemiological studies. I think that we must soon bring this issue to a close. But it is the moratorium that is being recommended by Congress, sir, that is up for discussion.

The FDA made its position clear earlier. We have tried to carry out very clearly the congressional mandate, and we feel, as I mentioned in the testimony, that we soon should resolve this issue.

Senator METZENBAUM. Now, Congress in the past provided the extension because there was no substitute. Diabetics and others who were in need of a substitute for sugar urged it upon the Congress, and I understand that.

Now we have a substitute called NutraSweet or aspartame, and there is some question about that. I wonder, if we provided you a relatively short period of time, what tests could be conducted by you; whether, A, you would do a new test on NutraSweet or aspartame, and how long that would take you, whether it could be done rather rapidly; and, second, whether there are not some additional tests that should be done at the present time with respect to saccharin and how long that would take and be done rather rapidly.

The Government usually moves very ponderously and very laboriously, but if we really were hell-bent for election or for passage of this legislation, whichever you want to call it, how fast could you get back to us with some further advice on both aspartame and the cyclamate study and the saccharin study as well?

Mr. YOUNG. First, in regard to the uses of saccharin, there are no complete substitutes for saccharin at this time. Aspartame will not substitute in some of the high-temperature uses. Therefore, I think it is unwise to say that NutraSweet is an overall substitute.

In regard to the direct answer to your question, the cyclamates will take up to approximately 3 years, as will other artificial sweeteners, from where we are today. We do not have a definite plan at this point on any particular sweetener.

In regard to additional information, we would be able to provide additional information in regard to some of the molecular markers and the relationship of this to human carcinogenicity, but I must emphasize that even if the ban were not extended, it would take a period of time for FDA to evaluate its action and then proceed through preliminary and final rulemaking, which would be, in itself, a couple of years' process.

Senator METZENBAUM. So what you are really saying is that even if we didn't pass the legislation, nothing catastrophic would happen the next day. You would still have to do evaluations and studies to determine whether or not you felt strongly enough about the 1977 studies to ban saccharin. Is that right?

Mr. YOUNG. Yes. With the most rapid action, it is 180 days to a year.

Senator METZENBAUM. So we don't have to have anything breathing down our backs and worry that if we don't do something by April 21, all hell will break loose.

Mr. YOUNG. I think a definite signal would be sent if nothing was done by April 21, and you might have a substantial concern.

Senator METZENBAUM. I think the lobbyists would be all over our backs. But let me ask you——

The CHAIRMAN. It might be more than the lobbyists. It might be a lot of people who need saccharin, and they would be screaming.

Senator METZENBAUM. Well, they still would get saccharin. He says it would take at least 6 months to a year before anything would happen from their standpoint.

Mr. YOUNG. But I think, though, Senator, it would be a great concern to not take into full account the health problems of some portions of the population, the diabetics and others, that do need artificial sweeteners, and there is no uniform substitute.

Senator METZENBAUM. I am aware of that.

Mr. YOUNG. I think the fear of this coming off rapidly might produce some degree of problem.

Senator METZENBAUM. Could we get some assurance from you that—as I understand it, there are no real studies going on of aspartame at the moment, and there are no real studies going on of saccharin at the moment. Is that correct?

Mr. YOUNG. No. There are ongoing studies on saccharin, and Dr. Hart will describe in great detail the NCTR study on saccharin. There are studies, I am sure, throughout the world literature that will be studying aspartame.

Senator METZENBAUM. And you say that the cyclamate studies will not be available for 3 years?

Mr. YOUNG. No. I said the approval would be likely—in answer to the chairman's question—we would be likely to have an answer within the 3 years. Dr. Miller, do you have a more concrete answer as to when we will get the study from the National Academy of Sciences?

Mr. MILLER. We will be hearing from the Academy, hopefully, by the end of April on the issue of carcinogenicity. If the Academy agrees that carcinogenicity is not an issue with cyclamates, there are still two other issues that have to be resolved, one of which is concerned with mutagenicity, and the other of which is concerned with testicular atrophy.

In terms of the former, there are some new studies which are being done, and we are supposed to receive them somewhere between November of this year and January of next year.

In addition, we have to look at some of the more recent data on testicular atrophy. So there is no—it would be impossible for me to say that we have a timetable for reaching this, but it will take us, as far as I can see, at least a year before we get all the data together and even decide whether we are going to approve it or not.

Senator METZENBAUM. Will those studies be made public as they come to you?

Mr. MILLER. Oh, yes. They always are, sir.

Senator METZENBAUM. And will the FDA followup on the CDC recommendations for clinical studies on NutraSweet?

Mr. YOUNG. We are looking at one particular study that is a controlled clinical trial that is being conducted by Searle, looking at some of the neurotoxicity, and there will be other studies that will be underway in regard to epidemiological studies on the one population subset that was identified.

Senator METZENBAUM. Will you meet the CDC recommendations?

Mr. YOUNG. I am sorry. I don't understand, sir.

Senator METZENBAUM. I think the CDC made some recommendations with respect to clinical studies, and I am asking whether or not the FDA will meet those recommendations.

Mr. YOUNG. We are actively exploring that. Dr. Miller, would you bring the Senator up to date on that?

Mr. MILLER. The CDC, as you know, suggested that we ought to explore the possibility that there may be some sensitive people in the population.

A study to try to identify and determine the mechanism of that population is the one that the Commissioner referred to, which is being done at Duke Medical School, and in which they are going to look at at least one of the most common of the reported effects of aspartame, which is headache.

That study is just getting underway. We are reviewing the protocols for that study. With the conclusion of that, if they can get a sufficient population, it should answer the CDC question.

Senator METZENBAUM. It should answer the CDC?

Mr. YOUNG. Yes, it should, and that is what is described as a double-blind study. It is a rather large study, as Dr. Miller alluded to, and it will be taken very seriously and done in collaboration with FDA looking at the protocols, as he stated.

Senator METZENBAUM. One last point that I want to get into, a short one. I have shown you these labels which are almost impossible to read. Could the FDA give Congress any assurance about your moving into the whole area—certainly, those do not conform with the language of the law. The language of the law is quite specific. Such statements—I think I read it before, talking about contrast by typography, layout, and color with other printed matter, and in conspicuous and legible type.

It just does not meet those requirements. Can we get some reassurance from you, Dr. Young, that you will move to explore this entire area to see whether or not, either on a voluntary basis, or more than that if necessary, see to it that the labeling be brought up to the language of the law?

Mr. YOUNG. I certainly will ask the Center to explore that, Senator, but it is important to emphasize that it is very difficult, even with larger amounts of resources than are available to the FDA, to study in depth all of the labels on foods. But we certainly will take this seriously and look into it and will report back to you.

Senator METZENBAUM. Well, let me say, Dr. Young, you know this idea about resources and stuff and having the problems with David Stockman not giving you—you don't have to have a 100-year study to look at some of those labels to know that they are not legible.

Now, you could probably have an Assistant Secretary go out and explain that—a male or female, either one—I don't want to indicate what kind of Secretary—but anybody can go and look at some of those labels and know that they are not legible. It is just so difficult to read them.

The CHAIRMAN. It depends on who is reading them, I suppose. Howard and I have a difficult time reading smaller print. [Laughter.]

I don't know what the reason for that is.

Senator METZENBAUM. If all four of you who wear glasses can walk over there and read every one of those labels, I will buy you dinner tonight. [Laughter.]

You cannot read that one on the blue.

Mr. YOUNG. Sir, I am sorry. The FDA is not allowed to take dinners from sponsors. [Laughter.]

Senator METZENBAUM. I don't intend to have to pay off. I don't have any problem. [Laughter.]

Thank you, Mr. Chairman.

The CHAIRMAN. Thank you, Mr. Commissioner.

Senator METZENBAUM. We have about 30 additional questions which we will submit, and I am sure they will be answered.

Mr. YOUNG. Please do so, and we would be happy to answer them to the best of our ability.

[The material referred to follows:]

SENATOR HOWARD METZENBAUM
QUESTIONS FOR FOOD AND DRUG ADMINISTRATION

1. According to a letter in the record, in 1977 FDA General Counsel Richard Merrill told Mr. James Turner and Dr. John Olney that if they still had concerns about the reliability of Searle's tests following a review by the Universities Associated for Research in Pathology (UAREP), "the Public Board of Inquiry on aspartame should provide a vehicle for a definitive resolution, at least for those studies about which you are most concerned."

   Yet Public Board of Inquiry documents show that both the FDA and Searle argued that the PBOI was not the proper forum for bringing up questions about the way the tests were conducted and those questions were not permitted. On what basis did the FDA decide to renege on this written promise?

2. Why did the FDA have the so-called Bressler team review three pivotal tests instead of having the group of college pathologists (UAREP) review all of them?

3. Why did FDA rely on test E 77/78 (brain tumor tests) when scientists reviewing the Bressler report concluded that "it cannot be determined with certainty whether the intended doses [of DKP] were in fact ingested [by the test animals]"? Add to this the fact that there was other evidence that the feed was not homogenous -- e.g., memos on test reports, an interview with former Searle employee Raymond Schroeder and

again, you have the question, given the fact that there were so many questions about the validity of this key test, why wasn't Searle asked by the FDA to repeat the test?

4. Memos in FDA's record show that FDA scientists who reviewed the Bressler report strongly recommended that the three pivotal tests they reviewed also be reviewed by UAREP because they apparently had such serious questions about what they had seen in the reports. Why wasn't their recommendation followed, and why wasn't UAREP asked to review these three tests?

5. Given the very serious concerns raised about the way Searle conducted animal testing, and the fact that aspartame would be widely available in the food supply, why didn't the FDA simply require Searle to repeat, at a minimum, the pivotal tests?

6. Why did the FDA choose to have UAREP determine if the tests were "actually conducted," as Commissioner Hayes put it in his decision to approve aspartame, instead of requiring Searle to repeat the tests?

7. In an interview with Common Cause Magazine, Kenneth Endicott, the head of UAREP, said UAREP's review did not necessarily mean the tests reviewed were "valid." He said, "there were lots of other opportunities for error" -- errors

that would not have been in the record UAREP reviewed. Yet the March 1976 FDA special investigative task force which looked at 11 aspartame tests found serious problems with laboratory practices, the quality of personnel, animal care, and the homogeneity of the feed given to animals -- all areas UAREP did not take responsibility for, according to Endicott. How did the FDA reconcile the serious problems raised by the task force -- not answered by UAREP -- with its decision to rely on those tests?

8. The March 1976 FDA task force investigation report said that "little concern was evidenced for the need of proper quality control of homogeneity, concentration or stability of the active ingredient-diet," and that because of inadequate practices at both Searle and Hazelton, "there is no way in which it can be assured that animals received the intended dosages." Given this conclusion, and the fact that UAREP also raised similar concerns, on what basis did the FDA decide that these concerns were resolved and that the tests therefore could be relied on?

9. The March 1976 FDA task force report raised questions about problems found in the designs of some of the aspartame tests. Did the FDA review the designs of all aspartame tests following the task force's report, and if so, please provide copies of the reports of these reviews.

10. In his decision, Commissioner Hayes said that because the 1975 FDA task force, whose report was issued in March of 1976, "only peripherally" involved aspartame, it was "superseded" by the UAREP review of the 12 pivotal tests and the Bressler review of three other tests. On what basis does the FDA conclude that the 1975 task force's conclusions "only peripherally" involved aspartame?

11. Documents submitted to the 1980 Public Board of Inquiry show that the Bureau of Foods relied on a number of tests -- E 38, 49, 52, 53, 54, 57, 63, 58, 59, 72, and 73 that were done during the time period when serious fundamental questions were raised about Searle's testing that were never reviewed by either UAREP or the Bressler team. On what basis did the Bureau of Foods determine that these tests were reliable?

    Please submit the written record showing how this decision that these tests could be relied on was reached.

12. In the FDA's denial of the Community Nutrition Institute's request for a hearing on aspartame, the FDA cites a number of tests that were done during the time period when serious, fundamental questions were raised about Searle's testing, yet these tests were never reviewed by either the FDA, Bressler team, or UAREP. These tests include E 15, 29, 37, 38, 42, 48, 50, 56, 57, 68, 71. On what basis did the Bureau of Foods determine that these tests were reliable?

13. Given the importance of the concerns raised by MIT's Dr. Richard Wurtman regarding aspartame's potential to affect brain chemistry, why wasn't the soft drink decision delayed so that his hypothesis could be more fully explored? Dr. Walle Nauta, head of the Public Board of Inquiry told Common Cause Magazine that Wurtman's hypothesis needs "extensive testing." He said the FDA should be following the issue with great concern. The science director of the National Soft Drink Association also told Common Cause Magazine that there was a reasonable basis for Wurtman's hypothesis and that it definitely should be pursued. In fact, in an NSDA draft objection to soft drink approval, the NSDA says that, "In light of the allocation of the burden of proof and the nature of the safety standard in food additive proceedings, FDA's handling of Dr. Wurtman's concerns was unusual. The tone of the July 9 notice suggested that the burden was on Dr. Wurtman to demonstrate that aspartame is harmful and that, absent affirmative demonstration of harm (which is obviously lacking at this point) aspartame must be approved. To the contrary, however, the burden is on Searle to prove a reasonable certainty that no harm to human health will result from aspartame." How do you respond, and what data did Searle submit to FDA to prove there was no validity to Dr. Wurtman's hypothesis?

14. Why wasn't the Bressler report made part of the public record before the Public Board of Inquiry was convened?

15. According to *Common Cause Magazine*, Searle submitted 13 tests to try to establish that aspartame would not cause genetic damage. Memos in the public record show that the FDA scientists who initially reviewed the tests found serious deficiencies in all of them, describing three as "incomplete individually and collectively."

Nevertheless, 1980 Public Board of Inquiry documents showed that although FDA officials acknowledged numerous problems with the tests, they decided that all the tests were good enough to rely upon in establishing the safety of aspartame.

How could the Bureau of Foods submit those tests as evidence of safety when the public record shows its *own* scientists who initially reviewed the tests found serious problems with them?

16. Memos obtained in a *Common Cause Magazine* investigation show that in 1973 the FDA's Bureau of Foods asked the Bureau of Drugs to evaluate ten clinical tests submitted by Searle to determine "whether safety problems might be anticipated should this sweetener be marketed for general use." Memos found in the public record show that Dr. Martha Freeman, then of the FDA's Bureau of Drugs, concluded that "the information provided is inadequate to permit an evaluation of potential toxicity of aspartame."

Although the FDA does not require clinical testing for proposed food additives, Freeman recommended that "marketing for use as a sweetening agent should be contingent upon satisfactory demonstration of clinical safety of the compound," which she told the magazine would require more rigorous testing.

She recommended that Searle's clinical testing be done under the Investigational New Drug (IND) regulations.

Given the potential widespread use of aspartame by the American public, why didn't the FDA take the added measure of requiring Searle to conduct its tests under the Investigational New Drug regulations, which would have given added assurance about any approval?

17. On what basis did the FDA Commissioner decide to approve aspartame when three scientists advising him said there were serious problems with the three cancerous brain tumor tests under consideration, identifying many of the same problems identified by other scientists over the previous ten years when the sweetener's approval was being considered?

For example, a May 19, 1981, memo from Robert J. Condon concludes, "I do not concur that aspartame has been shown to be safe with respect to the induction of brain tumors . . ." A May 18, 1981, memo from Satya D. Dubey, Ph.D., points out "certain statistical difficulties associated with E 33/34 and E 70 . . .", concluding after a lengthy analysis that "these studies are not confirmatory studies." Also, a May 19, 1981, memo from Douglas L. Park, Ph.D., concludes after a discussion of the brain tumor issue that "I believe that aspartame has not been shown to be safe for the proposed food additive uses. Along with the Board of Inquiry, I must recommend, therefore, that aspartame must not be approved until additional studies are carried out using proper experimental designs." Please explain in specific terms how these findings and conclusions were discounted for the approval.

18. A December 8, 1975, task force memo obtained by Common Cause Magazine states that this lifetime toxicity study (E 70) in rats was "the most pivotal" of the tests being investigated by the 1975 task force because "it was designed to show the no-effect level" of aspartame.

According to the memo, Richard Ronk, deputy director of the FDA's food safety division, said that if it were not possible to "reconstruct the tables from the raw data on the key study," then the FDA "would recommend revocation of the [Searle] petition" that aspartame be approved.

When UAREP reviewed the study, its report said that it had been "difficult to reconstruct and document the progression of the changes of the experiment . . . . This task was complicated by the fact that written instructions requested all earlier versions of protocols [research plans] be destroyed as they were updated."

Given the fact that UAREP had difficulty reconstructing this "most pivotal" test, and given the widespread potential use of aspartame, why wasn't Searle required to repeat this test so there could be total confidence in the results of the test?

19. In documents submitted to the 1980 Public Board of Inquiry, the FDA said that "in consideration of the remote possibility that a parent might use aspartame as a non-sugar sweetener in the infant formula or food, there may be some merit in the inclusion of a statement on the label to the effect that aspartame and aspartame-containing foods are not intended for use in infant feeding. Such labeling may provide added assurance that aspartame will not be fed to infants." Given the fact that it is not at all unlikely that parents might use aspartame in baby or infant foods, on the assumption that it is superior to sugar (in terms of the health of their baby), why didn't the FDA require a warning that aspartame should not be used in infant feeding?

20. In his 1981 decision, Hayes said "the available data establish" that the maximum projected consumption of 34 milligrams per kilogram of body weight is "still far, far below any level even suspected of being toxic." What does the FDA consider the toxic level to be?

21. In his 1981 decision, Hayes also says that the "safety assessment on the brain damage issues is tied closely to projected aspartame consumption levels." Therefore, what is the level at which aspartame causes brain damage?

22. In a letter to the FDA, Dr. William Pardridge, associate professor of medicine at the University of California, Los Angeles, wrote to the FDA saying that instead of asking at what level would aspartame cause brain damage, the FDA instead should have asked if high dose aspartame would "cause subtle changes in brain development." Did the FDA address this question and if so, how? Are you certain high dose aspartame consumption will not cause subtle changes in brain development?

23. Dr. Pardridge also wrote about the possibility that women with a phenylalanine intolerance who consumed large quantities of aspartame (50 milligrams per kilogram of body weight) might give birth to infants with a "10 to 15 percent drop" in IQ levels. He said in his letter that he believes there "are 20 million individuals in the country with phenylalanine intolerance," many of whom may be unaware of their condition. How does the FDA respond to this concern articulated by Dr. Pardridge?

24. The FDA's soft drink approval indicates that under moderate conditions, extensive decomposition of aspartame may occur in soft drinks, yet Searle is unable to account for more than one-third of the chemicals to which aspartame decomposes. Why didn't the FDA require Searle to identify these chemicals? How can the FDA conclude aspartame is safe without having identified these remaining chemicals?

25. Dr. C. Keith Connors of Children's Hospital in Washington told The New York Times recently that he is worried about aspartame's effects on certain highly sensitive individuals. He said he has studied two young children who suffer extreme agitation following doses of aspartame equivalent to the amount found in a six-ounce serving of Kool-Aid sweetened with NutraSweet. One of the children becomes so agitated he has to be restrained, Connors said. The other, who is sensitive to sugar, becomes even more agitated when given aspartame, he said. Have you consulted with Dr. Connors about his findings? Has anyone at the FDA viewed the videotape he reportedly has showing the children's reactions? How do you view his findings?

26. The Centers for Disease Control report on aspartame states that the only way to determine whether individuals may be sensitive to aspartame-containing products is through focused clinical studies and that the highest priority "might be in the neurological/behavioral area, focusing on such symptoms as headaches, mood alterations, and behavior changes." Have you required Searle to perform such studies? What follow-up work have you done on the CDC findings?

27. In a January 10, 1977 letter from FDA General Counsel Richard Merrill to Samuel K. Skinner, U.S. Attorney of the Northern District of Illinois, the FDA makes reference on page 18 and later on page 20 to "approximately 150" studies used by the FDA to determine aspartame's safety when FDA gave notice July 16, 1974 that aspartame should be approved. Please enumerate by E number the 150 studies used for this decision.

28. On page 32 of the same letter referred to above, reference is made to exhibit 21, which includes comments by Dr. Dutt, former head of the Mathematics-Statistics Department, regarding Searle's statistical and sampling methods. Please provide a copy of this exhibit.

29. Please identify all contacts with both Reagan and Carter White House officials regarding approval of aspartame. Please include a paragraph explaining the nature of the contacts. This should also include contacts with the Reagan transition team.

30. Please provide copies of all memos, communications, and recommendations from the Reagan FDA transition team, including all those which refer to the approval of aspartame.

31. On page 65 of the March 1976 report of the Searle Investigative Task Force, reference is made to a July 15, 1975 letter to Searle from one of its consultants on reproduction and teratology. Please provide a copy of this letter.

32. Please provide copies of any letters or other communications written following FDA's request of January 10, 1977 for a grand jury investigation of Searle asking for an explanation of why no indictments were handed down regarding Searle's testing.

33. Regarding the January 10, 1977 letter to the U.S. attorney referred to above, please provide copies of a record of a meeting held May 18, a copy of Searle's written reply to the task force report on May 21 and the June 21, 1976 memo from Searle to the FDA -- all referred to on page 5 of the letter.

34. Please provide a copy of the December 28, 1970 memo from Mr. Helling of Searle entitled, "Food and Drug Sweetener Strategy" referred to on page 26 of the January 10, 1977 letter from FDA General Counsel Merrill to U.S. Attorney Samuel Skinner.

35. Please provide copies of all complaints received by FDA or Searle regarding aspartame since May 1984 to the present.

SENATOR CHRISTOPHER DODD
QUESTIONS FOR FOOD AND DRUG ADMINISTRATION

36. Can you give us a brief outline of limitations entailed in extrapolating from findings based on experiments with laboratory animals to conclusions about effects on human beings?

37. Other things being equal, if a particular substance, such as saccharin, has different effects on different types of laboratory animals, doesn't this call into question the relevance of animal study findings to humans?

SENATOR CHARLES GRASSLEY
QUESTIONS FOR FOOD AND DRUG ADMINISTRATION

38. You mentioned that you are planning follow-up research on this issue. You also noted that you recognize that at some point we must answer the issue definitively. Are you able to say how long it will take before we have some definitive results, or are there too many imponderables in the research process to state with any reliability when you might have such results?

39. Does FDA currently have work underway to test the safety of saccharin substitutes, and what does FDA plan to undertake with respect to aspartame and other substitutes?

(EDITOR'S NOTE: In the interest of economy, the answers supplied to the Committee by the FDA in response to questions by Senator Metzenbaum and others were retained in the files of the Committee because of the voluminous content of the material supplied.)

The **CHAIRMAN**. And we are hopeful that most of the questions for other witnesses will be submitted to them as well, or we will never get through.

Thank you, Mr. Commissioner. We appreciate you and your colleagues for being here. We appreciate your patience.

Senator **METZENBAUM**. Mr. Chairman, I know that I was very lengthy in my questioning, but I also would like to point out that Dr. Wurtman and Dr. Arnold are here from long distances. Dr. Arnold, I guess, is on our next panel, from Canada, and I wonder if we could put Dr. Wurtman on the panel as well. Would that be possible? He is from Massachusetts.

The **CHAIRMAN**. At this point, no, because I have got every witness here who has got a schedule, and some are from out of town, and some have to catch planes.

We are going to limit each witness from here on in to 5 minutes, and that is it. I am going to be firm about cutting off remarks. As far as I am concerned, I hope we will limit our questions to the most pertinent questions so that we can get through sometime today.

Our next panel will be Dr. Schoenig from Annapolis, MD; Dr. Ronald Hart, Director of the National Center for Toxicological Research for the FDA in Little Rock, AR; and Dr. Douglas Arnold, Toxicology Research Division, Health Protection Branch, Health and Welfare in Ottawa, Canada.

Could we have order?

Now, we understand that Dr. Hart has to catch a plane, so, doctor, we are going to accommodate you and allow you to go first. Then we will go to Dr. Schoenig, and then we will go to Dr. Arnold.

We are going to put all statements in the record as though fully delivered. If you can summarize in less than 5 minutes, this particular chairman will be very grateful, because I have to rearrange my whole schedule. If you cannot, I am going to cut you off in 5 minutes, and then we will start questioning.

Go ahead, Dr. Hart.

STATEMENT OF RONALD HART, PH.D, DIRECTOR, NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH [FDA]

Mr. **HART**. Mr. Chairman, it is indeed a pleasure to have the opportunity to testify before the Committee on Labor and Human Resources.

If I might, I would like to submit my statement for the record and summarize it.

The **CHAIRMAN**. Without objection, all statements will be put in the record.

Mr. **HART**. Saccharin, while simple in structure, is extremely complex relative to its action. The summary of what we have found thus far is as follows: That in one species, namely the rat, under conditions which are somewhat unique in the fact that they involve exposure of the animal to a replicating cell population called the epithelium, which is essentially one of the layers of the bladder, that saccharin will prove itself to be a carcinogen.

Senator **METZENBAUM**. Would you repeat that sentence? There was noise in the room.

Mr. **Hart**. That what we have thus far found that could be summarized is that saccharin, in one species, namely the rat, under a unique set of circumstances, where the saccharin is given to the animal during a period when the bladder epithelium, which is one of the layers that compose this balloon called the bladder, is replicating, namely during embryogenesis, during fetal development; or from the beginning of birth, from the first day after birth, for the entire lifespan, it will be a carcinogen.

It is not a carcinogen in what we call our standard chronic bioassay, which we normally use for testing agents to decide whether or not they are carcinogenic.

Saccharin also, under those situations or conditions where it is given following challenge by what is called an initiator, which was described earlier, will again, in the rat, promote the number of tumors seen from that initiating agent and therefore is termed a promoter. It enhances the number or brings forth in time the time to tumor occurrence, and again, that is in the rat.

Now, that seemed to be a fairly interesting finding, because proliferation of the cells seems to be the key factor in both cases. For example, as an initiator or as a complete carcinogen, saccharin had to be present when the cells were dividing in this layer called the epithelium of the bladder.

Also, saccharin had to be acted on as a promoter only if the bladder epithelium was damaged, in other words, by parasites, by putting a cryogenic probe—that is a very cold stainless steel probe—onto the bladder epithelium, thereby causing blistering, or when you have a challenge beforehand with a complete agent called an initiator.

However, when we looked at mice, what we found was something quite different. In the case of mice, we found that saccharin was not a carcinogen, and it was not a promoter, and in fact, in the newborn mouse assay, where you delivered saccharin from day one after birth on through the lifespan, again, it was not a carcinogen.

In fact, in the initiation/promotion studies, it was an antipromoter. In other words, it actually decreased the number of tumors induced in the liver by a very potent chemical carcinogen called acetoxyacetomenofleury, AAF.

Now, we said, well, gee, this is kind of confusing, because in one case you have a situation where saccharin is acting as a promoter and a carcinogen—namely, the rat—and in the other species, it is not acting as a carcinogen; it is acting as an antipromoter.

So we next looked at human cells in culture. Now, what this essentially is is where you take a small biopsy from the skin, for example, and you put those cells into culture. In other words, the culture dish might look something like this, and you put them into the dish, and you put the media on it, which will allow them to divide or grow.

Next, we said, well, we will look at saccharin as a promoter in this condition. It was not a promoter. Well, was saccharin an initiator of human cells? Did it transform these human cells to a form that when you take them out of the dish and put them into an animal, were they acceptable? In other words, in a mouse, would they form tumors? And the answer was no, they were not an initiator.

However, when you applied the saccharin concurrent with the initiator, you could transform the human cells. So now we have a situation where we have one species which is sensitive, one species which is refractory, and man seems to be acting by a different set of circumstances than either of the other two species, and it is extremely difficult under those circumstances to extrapolate animal data to human health effects.

[The prepared statement of Dr. Hart follows:]

STATEMENT
BY
RONALD W. HART, Ph.D.
DIRECTOR
NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman:

I am pleased to have this opportunity to testify on the studies that have been conducted by the National Center for Toxicological Research (NCTR) into the carcinogenicity of saccharin.

At the time Congress originally passed the moratorium on the Food and Drug Administration's action to ban saccharin, several studies had shown that high doses of saccharin given in the diet to rats through two generations resulted in the development of tumors in the urinary bladder. Since that time, other scientists have shown that the same high doses of saccharin (3 to 7.5 percent in the diet) can cause bladder cancer in rats in a single generation if the saccharin treatment is begun immediately after birth, or if the bladder receives prior damage due to mechanical injury or to infection by parasites. Each of these studies indicate that at high doses under specific experimental conditions, saccharin by itself can cause bladder cancer in rats. Thus, scientists often refer to saccharin as a weak, but complete, carcinogen in rats.

At the same time these studies were underway, scientists were beginning to show that saccharin also had the properties of a "tumor promoter." Now, a tumor promoter is a substance that by itself shows little or no carcinogenic activity but, if it is given to animals after a subcarcinogenic dose (called an initiating dose) of a strong carcinogen, a high yield of tumors or a shortened time-to-tumor occurrence will occur. In this regard, saccharin has now been shown to promote bladder cancer in rats previously given bladder carcinogens in low doses in the diet, in the drinking water, or even instilled directly into the urinary bladder. It has been suggested that the results obtained showing saccharin as a complete carcinogen (i.e., able to cause cancer by itself) could be explained if some unknown exposure to an initiating carcinogen were really occurring, but this question remains unresolved.

We at the National Center for Toxicological Research of the Food and Drug Administration decided to examine the effect of saccharin as a tumor promoter in rats when given at several doses ranging from 0.1 percent to 5 percent. To accomplish this, our rats were first given a low dose of a strong carcinogen applied directly to the urinary bladder. In this study, saccharin caused a more rapid development of bladder tumors in rats given the initiating carcinogen, while saccharin administered by itself, without the initiating carcinogen, had no ill effects. The increase in the "time-to-tumor" was a straight-line relationship with increasing saccharin doses between 0.1 and 2.5 percent. At 5 percent, however, we exceeded the maximum tolerated dose and apparently caused tumor development to be suppressed. I must emphasize that we do not yet know whether the mechanism of action of saccharin in rats is similar to that in humans.

In order to gain a further insight on the effects of saccharin in different species, we designed a very similar initiation-promotion experiment in mice. These results clearly showed that saccharin was completely ineffective either as a complete carcinogen or a bladder tumor promoter. In addition, when we gave mice several doses of a carcinogen that caused liver tumors, saccharin inhibited liver tumor development. Thus, in rats, saccharin was positive as a tumor promoter, or carcinogen, while in mice it was completely negative.

These findings, which have just recently become available, now pose a new question. Are humans more like rats or more like mice in their sensitivity to the effects of saccharin? We have not yet answered this question. However, our initial experiment using cultured human skin cells indicates that saccharin is very effective at very low doses in enhancing the transformation of these cells into malignant cancer cells, provided the cells also recieve a strong carcinogen in a dose too low to yield transformed cells by itself. Preliminary experiments further suggest that saccharin's mechanism of action in the cultured cells may be related to its ability to replace insulin as a necessary growth factor. However, until this mechanism is fully elucidated at the molecular level, we cannot be certain that it is operative in humans who consume saccharin.

In summary, saccharin appears to act as a carcinogen or tumor promoter in rats, but not in mice, and may actually inhibit tumors in this system. Our future research plans involve experiments to determine saccharin's mechanism of action in cultured human cells and see if it is similar to the rat model. Depending on the answers we get, it should then be possible to more accurately assess the degree of human risk posed by saccharin. To date, science has not provided any simple answers to the complex action of saccharin. However, considerable progress has been made in our scientific understanding of the problem and we hope that substantial progress will be forthcoming.

This concludes my formal testimony. I will be pleased to answer any questions you may have.

The CHAIRMAN. Thank you, Dr. Hart. Your 5 minutes are just about up.

Let me just ask one question, and I will submit my other questions in writing to you. Do you feel, Dr. Hart, that the evidence on saccharin at this point shows that it is a sufficient risk to the public to require its removal from the public market?

Mr. HART. In my personal opinion?

The CHAIRMAN. That is right. Well, in your scientific opinion.

Mr. HART. At this point, I think the data is inconclusive relative to a human risk, because the human epidemiological studies are not showing anything that would be positive.

I also believe that there are sufficient studies under way at this time, now using human cells in culture, and collateral studies with rats again, to make better determinations probably within the next 2 to 3 years.

The CHAIRMAN. So you are saying that over the next 3 years we should have a better determination or at least better data upon which to base a definitive conclusion here?

Mr. HART. Again, I would like to point out—and I think this is terribly important, Senator—that saccharin is not acting like most chemical carcinogens that we know. It simply is a very complex—it is acting through very complex mechanisms which may or may not be species-specific, and that is the problem that we are facing.

The CHAIRMAN. Senator Metzenbaum.

Senator METZENBAUM. Dr. Hart, I think you also have an Ohio background, do you not, sir?

Mr. HART. And I am very proud of being a Buckeye, having been on the campus for almost a decade.

Senator METZENBAUM. It is nice to have you with us today.

Is it not the fact, Dr. Hart, that in the studies you made, that as you increased the dosage with the rats, the incidence of cancer also increased? I think that chart may indicate the saccharin dosage as well as the proportion of animals with bladder tumors.

Mr. HART. Can I explain the chart a little bit further, Senator?

Senator METZENBAUM. Please do. I am sure you understand it better than I do. [Laughter.]

Mr. HART. Well, these studies were performed by one of my, I think, very competent scientists at the Center, Dr. Kadlibaugh, and not by myself. I simply act as the director of the Center, and I guess that means I am neutral enough that I can walk between the lines of our scientists.

Essentially, in that study that you are seeing up there, the first prerequisite that you have to have is that you have to give a dose of known strong carcinogenic agent, in this case called MNU. In the case of the mice we used AAF. That is a dose just barely below the dose to induce a large number of tumors in the animal.

You have to quantitate that, which we did, by going in and doing all sorts of molecular biology to actually measure how many damaged sites there were in the DNA, and that is a very interesting technique in its own right.

You then follow up by giving saccharin for a protracted period of time at the doses shown up here, which go from 0.1 up to 5. The next step is that you then look at the occurrence of tumors.

So, being terribly specific, and this sounds terribly like cutting of hairs, but I know lawyers are probably not used to cutting hairs in the definition of words at all.

The **Chairman**. No, we split them. [Laughter.]

Mr. **Hart**. But the point here is that saccharin in this case was looked at as a promoter, not as a carcinogen, as an agent which enhanced the number of tumors, not an agent which actually induced the tumors per se. In fact, under this experimental design, saccharin does not induce tumors by itself, only with the presence of an initiator preceding the saccharin.

Senator **Metzenbaum**. As I understand it, was there any dosage that you could find below which it did not promote a tumor?

Mr. **Hart**. This comes to the point that the study up there shows, that down to the doses that we tested, saccharin was a promoter. Now, below those doses, you would have to have a larger and larger and larger experiment with more and more animals to test increased sensitivity.

Senator **Metzenbaum**. Now, when we are talking about initiator or promoter, the promoter problem can be equally as great as the initiator as far as the safety of humans is concerned, because when they are ingesting the saccharin, we are not exactly sure what other products, what other items, it can meet in the stomach and cause carcinogen to develop. Is that not correct?

Mr. **Hart**. That is an excellent point. The difficulty is that we do not know the mechanism by which promotion occurs. It has been hypothesized—and there is some fairly good evidence—the promoters, these other agents, have a threshold, in other words, a level below which they do not promote.

There is also an equally large school of thought which says that promoters have no threshold. That is still a question very much up in the air.

The thing which is interesting relative to these studies, however, Senator Metzenbaum, is the fact that, going back to the proliferation requirement for saccharin, one of the things that promoters do is they cause enhanced proliferation as a result of trying to do the punishment of cells which are oftentimes damaged.

So if you take that scenario of how a promoter works, then what you say is that the promoters would have a threshold which would be based on the level of damage required to have proliferation or replacement of cells.

Senator **Metzenbaum**. You concluded in your report, as I understand it—or perhaps it was the FDA that concluded—Nonetheless, the best of the data is strong enough to conclude that saccharin is a promoter for bladder cancer in the rats, perhaps down to levels of ⅒ of 1 percent.

Mr. **Hart**. That is correct.

Senator **Metzenbaum**. And that is part of the problem. At this point, we really do not know with what other substances the saccharin can combine in order to cause cancer in the human body.

Mr. **Hart**. Well, the answer, I think, to that is that for the rat, it is a promoter; for the mouse, it is actually an antipromoter; and for the humans, it does not seem to act as a promoter, at least for human cells in culture. It also does not appear to act as an initiator for human cells in culture, but it only works when the initiator and the saccharin are given concurrently under a very unique set of circumstances.

Senator **Metzenbaum**. We cannot get too much comfort in finding that it does not have an impact on human cells in culture, because there are many studies that indicate that what does not work in culture does work in the human body.

Mr. **Hart**. That is very true, and vice versa as well.

Senator **Metzenbaum**. Yes.

Let me quote you from an FDA document which summarizes the findings of over 170 studies which have been published on saccharin since the 1977 moratorium: "Waiting for as long as 6 weeks after exposure to an initiator before promoting with saccharin does not cancel saccharin's promotion activity." In layman's terms, what does that mean?

Mr. **Hart**. That means, as for most promoters, there is a window between the time that you have been subject to an initiator and the time that you can follow up with the agent which is called a promoter, and it will still enhance, though at a decreasing level, the number of tumors above what you would normally expect to see with the initiator alone.

Senator **Metzenbaum**. Dr. Hart, when may we expect some further reports on the tests that you are presently conducting in connection with saccharin?

Mr. **Hart**. Well, some of the tests, such as the human cell studies that we have just begun, we will have results coming out from those studies within the next 12 to 18 months. Relative to the cocarcinogenicity study in the rat—in other words, to find out if the rat is acting like the human rather than necessarily the human acting like the rat—they will take about 2 to 2½ years.

Senator **Metzenbaum**. So within 12 to 18 months, we will have some results in connection with studies on humans?

Mr. **Hart**. Additional results on relation to human cells in culture, yes.

Senator **Metzenbaum**. Thank you, Dr. **Hart**.

The **Chairman**. Thank you. Dr. Schoenig.

Senator **Metzenbaum**. Oh, one question.

The **Chairman**. Surely.

Senator **Metzenbaum**. Do you use saccharin?

Mr. **Hart**. I have used saccharin. I also tend to use NutraSweet. Yes, sir.

Senator **Metzenbaum**. Would you permit your children to ingest the saccharin or NutraSweet on a regular basis?

Mr. **Hart**. My 21-month-old daughter does so.

Senator **Metzenbaum**. Does so?

Mr. **Hart**. Through soft drinks, yes.

Senator **Metzenbaum**. Through what?

Mr. **Hart**. Through soft drinks, yes.

Senator **Metzenbaum**. Is that for any particular reason or just because she likes the taste? I mean, is it for any health reasons?

Mr. **Hart**. No. I happen to believe that restricting caloric intake is very beneficial, within limited degrees of a balanced diet. So I do use them, and so does the rest of my family, both NutraSweet and saccharin. My grandmother was a diabetic, and as a consequence, both myself and my daughter are prediabetic in nature.

Senator **Metzenbaum**. That is reassuring. Thank you.

The **Chairman**. Dr. Schoenig.

STATEMENT OF DR. G.P. SCHOENIG, TOXICOLOGY CONSULTANT

Dr. **Schoenig**. I appreciate the opportunity to be here, and I will try to summarize as best I can. In the time I have, I will try to describe the rationale, the design, the results, and the interpretation of the large industry-sponsored study which has been referred to earlier today as the IRDC study.

The noncaloric sweetener sodium saccharin has been evaluated in many carcinogenicity studies which have used mice, hamsters, rats, and monkeys as test animals. Most of these studies were single-generation, long-term feeding studies in which no increase in tumor incidence was observed.

However, in three of these studies conducted in rats, which were two-generation bioassays, a significant increase in urinary bladder tumors was observed.

While the findings in these studies demonstrated that the feeding of high dietary concentrations of sodium saccharin was somehow related to the occurrence of urinary bladder tumors in male rats, they did not define the dose response for urinary bladder tumors nor the mechanism by which these tumors occur.

Therefore, the purposes of the IRDC study, which involved the study of 2,500 second-generation male rats, were to determine the dose response for urinary bladder tumors in male rats and to evaluate other physiological or pathological changes which may be related to the occurrence of these tumors.

In this regard, it is important to note that the occurrence of urinary bladder tumors in this study at dietary concentrations somewhat below those which had been previously reported was not an unexpected finding but was a predictable event based upon the tumor incidences at sodium saccharin dietary concentrations of 5 and 7.5 percent in previous bioassays.

The **Chairman**. Excuse me just a second. Dr. Hart, if you need to catch your plane, we would be happy to let you go at this time.

Mr. **Hart**. I appreciate that. Thank you, Senator.

The **Chairman**. Of course.

Senator **Metzenbaum**. Thank you, Dr. Hart.

Dr. Schoenig, you are reading so rapidly that I am wondering whether or not you could put your notes away, submit your whole statement, and just tell us what you are saying, because you are going too fast for me to absorb it. Even when you go slowly, I have trouble.

Dr. **Schoenig**. I am sorry. I guess I wanted to make sure I didn't get cut off in the 5 minutes.

The **Chairman**. Well, a summary is just as good.

Dr. **Schoenig**. Well, that is what I was planning on doing. I probably don't have to go quite as fast.

The **Chairman**. All right.

Dr. **Schoenig**. The main point that I tried to make there in that few moments is that there had been three previous studies conducted on sodium saccharin which showed that bladder tumors did occur in male rats at dose levels of 5 and 7.5 percent. This study was not conducted to refute those findings but to try to help define the dose response to urinary bladder tumors to determine if it was a very steep response or a very shallow response, which is a very important item to know in assessing the human risk of saccharin, and also to try to determine whether the physiological changes that have been observed in these animals at the same dose levels were related to the occurrence of the tumors.

I will now get into the results of the study. The objective of determining the nature of the dose response for urinary bladder tumors was achieved. This response was very steep, indicating that the tumor rate declined very rapidly with a decrease in dose.

The question of the no-effect level, which was discussed earlier today, was addressed by performing traditional pairwise comparisons between the saccharin-treated groups and the untreated control group. At sodium saccharin dietary concentrations of 3 percent and above, statistically significant differences were found between the control group and the untreated control group.

However, regardless of how the data were analyzed statistically for the 1-percent level, the tumor incidence at this dietary concentration was not statistically significantly different. However, as Dr. Flamm mentioned, 5 of the 700 rats in the 1-percent sodium saccharin treatment group did develop bladder tumors, while there were no bladder tumors observed in the 350 control animals.

Therefore, the background tumor incidence for this strain of rat was reviewed in 863 male control rats from 10 other *in utero* studies which were conducted at the same laboratory. It was found from this review that the background tumor incidence in the control animals at IRDC was exactly the same as that observed in the 1-percent level in the IRDC study that I am describing, and that level was 0.8 percent.

An additional evaluation of the bladder tissues from the study was also commissioned by the sponsor. Dr. Robert Squire performed this additional evaluation. Dr. Squire examined the tissues without knowledge of treatment group and used his standard criteria for diagnosing and grading the lesions. On the basis of his independent evaluation, Dr. Squire concluded that there were no compound-related effects evident at the 1-percent level.

The major underlying motivation for conducting this bioassay was to obtain information which addressed the question whether or not the tumors which occur in sodium saccharin-treated rats are a high-dose phenomenon which only occurs secondarily to changes in physiology. No other information, short of determining the mechanism by which the tumors occur, was considered to be as potentially useful in helping to evaluate the safety of sodium saccharin in humans.

In this regard, the steep dose response and the demonstration of many physiological changes at the same high dose levels where tumors are observed support the concept of a high-dose phenomenon mediated through physiological changes.

The information obtained in this bioassay should not only be useful from a conceptual point of view in evaluating the potential risk of sodium saccharin in humans, but the data base will also be useful in mathematically estimating the risk at lower dose levels if one elects to use data from laboratory animals for this purpose.

The larger data base will provide much more confidence in any estimate of risk that is made. It should also be useful in selecting appropriate models for risk extrapolation. In this regard, the biology, the large amount of data in the observed range, and the steep dose response suggest that the use of any risk extrapolation model with a linear term is probably overly conservative. This is supported by the fact that the data overwhelmingly reject the one-hit model in a statistical sense.

However, regardless of which risk extrapolation model is used, any estimate of risk that is calculated using these data will be less than that obtained using the data base which existed before this study was conducted.

[The prepared statement of Dr. Schoenig follows:]

Testimony of Gerald P. Schoenig, Ph.D.

Consultant in Toxicology
1603 Bay Ridge Avenue
Annapolis, Maryland 21403

to the Committee on Labor and Human Resources
United States Senate

on Saccharin Study and Labeling Act

The purpose of my testimony is to discuss the rationale, design and results of a large industry sponsored study which was undertaken on the artificial sweetener sodium saccharin (NaS). While in my role as a toxicology consultant, I was hired by the sponsor of this study to help design and monitor it, my testimony represents my own personal and professional opinion and does not necessarily reflect the opinion or position of the study's sponsor or the industry which supported it.

Since the study was conducted at International Research and Development Corporation, it has most often been referred to as the IRDC sodium saccharin (NaS) study. I will also refer to it as such in this testimony. Prior to the start of the IRDC NaS study, 15-20 long term feeding studies had already been conducted on NaS. Rats, mice, hamsters and monkeys had been used as test animals in these studies. With the exception of three two-generation feeding studies in rats, no increase in tumors was observed in these studies. In the three two-generation rat studies, an increase in bladder tumors was observed in male rats at dietary concentrations of 5.0 or 7.5%. Since the tumors were only observed at these very high dose levels and since a number of other physiological changes were also observed in rats at these high levels, there was good reason to question whether or not the tumors were a result of the direct action of the saccharin molecule or an indirect effect of altered physiology. The importance of this distinction was key in designing the IRDC NaS study and is also key in evaluating the safety of NaS for humans. The reason for this is because it is a generally accepted principle of toxicology that a threshold dose below which no-effect will occur exists for agents which modify the physiological status of a biological system. In the case of NaS, if it can be reasonably demonstrated that the tumors occur secondarily to changes in physiology and that the threshold dose for the physiological effects observed in laboratory animals is sufficiently above the levels of human consumption, one can reasonably assume that the physiological effects and the resultant increase in tumors will not occur in humans. At the opposite end of the spectrum is the theory that even one molecule of a tumor agent which acts directly on the genetic material of the cell can cause a tumor.

In addition to the fact that many physiological changes were observed in male rats at the same dose levels where bladder tumors are observed, it was also known prior to the start of the IRDC NaS study that NaS did not possess other characteristics generally attributed to direct acting carcinogens. Of particular importance it had been shown that NaS was not metabolized and that NaS did not bind to the genetic material of the cell. In many respects, NaS is very similar to ordinary table salt (NaCl). Both materials are salts of strong acids. NaCl is the salt of hydrochloric acid (HCl). NaS is the salt of saccharinic acid. Both are made up of a positively charged and a negatively charged ion. The positively charged ion is the same for both materials, i.e. sodium (Na+). In the case of NaCl, the negatively charged ion is chlorine (Cl^-) while the negatively charged ion in NaS is a chemical entity made up of several different atoms. While the chloride ion and the saccharin ion have different chemical structures, they are handled very similarly in the body, i.e. they are absorbed from the gut and excreted unchanged by the kidney into the urine. One difference between ordinary table salt and NaS is that NaS is less toxic. This is evidenced by the fact that higher dietary concentrations of NaS can be evaluated in long term feeding studies such as those in which an increase in tumors have been observed. In this regard it is interesting to note that if the rats fed NaS at dietary concentrations of 5.0 or 7.5% in the earlier bioassays would have died, there probably never would have been a NaS controversy. People would not have been concerned since the feeding of ordinary table salt would have produced the same results. A lower dose of NaS would have then been used in the long term feeding studies and with the number of rats normally used in these studies no bladder tumors would have been observed and that would have been the end of it.

The National Academy of Sciences (NAS) had also reviewed the NaS data base prior to the start of the IRDC NaS study. As part of their review they identified deficiencies in the data base and made a number of suggestions for research which would help in the assessment of NaS's safety for humans. Some of the areas where they recommended additional work were to obtain more reliable data on the dose response for bladder tumors in male rats and to investigate the role of physiological changes and *in utero* exposure in the occurrence of the bladder tumors. The additional information on dose response was considered important because it was virtually impossible to extrapolate to the lower levels of human consumption from the higher levels fed to male rats with any real degree of confidence from the existing data base. For example, the estimates of risk extrapolated from the data in the three earlier positive two-generation rat studies ranged from an increased bladder cancer risk of one in a thousand to one in a billion. This is not very useful information for making a decision regarding the safety of any material. The information on physiological changes was considered important because, as I mentioned earlier, if the tumors were shown to be a result of increased altered physiology the likelihood of NaS being a hazard to the human population would be remote. The data on *in utero* exposure was considered important because of the potential for pregnant women to consume NaS containing beverages and foods.

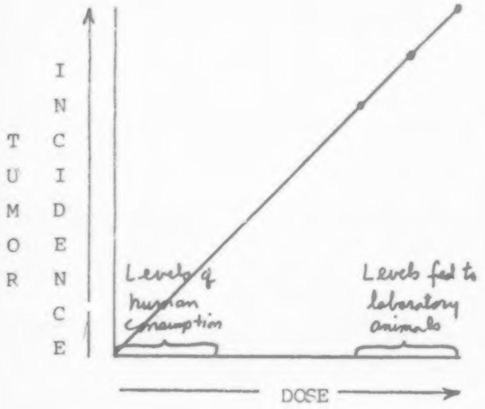
Therefore, consistant with the recommendation of the NaS, three of the major purposes of the IRDC NaS study became to define the dose response for bladder tumors in male rats and to evaluate the roles of physiological changes and *in utero* exposure in the occurrence of the tumors. A number of experimental designs were considered and input into the design was solicited from government, academic and industry sources. After considerable deliberation and thought, the study was designed in an unbalanced manner in which larger numbers of animals were placed at the lower dose levels where the tumor response was expected to be lower. Consideration was given to using only two groups of animals, i.e. one control group and one group fed NaS at a dietary concentration of 1.0%. However, this design would not have provided any information as to the shape of the dose response curve and a negative response could always be interpreted as negative only because not enough animals were tested. It is interesting to note that this interpretation has already been given to the 1.0% dose level in the IRDC NaS study even though 700 rats or 14 times the normal number of rats used in traditional carcinogenicity bioassays were evaluated at that level. In addition to the dose response portion of the bioassay, three other groups, each consisting of 125 second generation male rats, were included in the study. Animals in two of these groups were used to evaluate the role of *in utero* exposure and the animals in the third extra group were used to evaluate the role of sodium and/or the specificity of NaS in the occurrence of bladder tumors. Animals in the latter group were fed sodium hippurate (NaH), a compound which has a number of physical and chemical properties in common with NaS. Unfortunately, because of unexpected toxicity, the dose level of NaH had to be reduced from the scheduled 5.0% to 3.0% reducing its value for comparative purposes. The actual study design is shown below:

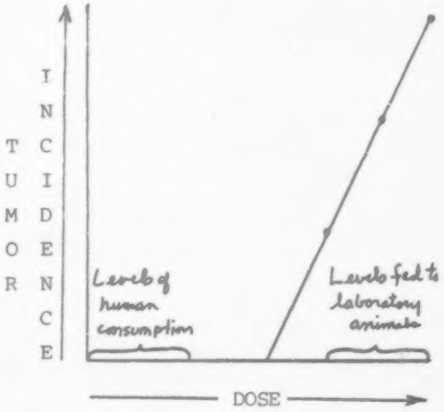
STUDY DESIGN OF IRDC SACCHARIN BIOASSAY

Group	Number of Second Generation Male Rats/Group
Control	350
1.0% NaS	700
3.0% NaS	500
4.0% NaS	200
5.0% NaS	125
6.25% NaS	125
7.5% NaS	125
5.0% NaS (during gestation)	125
5.0% NaS (following gestation)	125
3.0% Sodium hippurate	125
Total	2500

Another important point concerning the intent and the dose level selection in the IRDC NaS study is that the occurence of bladder tumors at the 3.0% NaS dietary concentration was not an unexpected finding, but an event that was very predictable based upon the tumor data from the three previous positive two-generation bioassays. It was also an event which was considered necessary to define the dose response curve. Therefore, to interpret the results of the IRDC NaS study simply as confirming the tumor data in the previous studies or showing that bladder tumors occur at levels lower than reported before is not consistent with the intent of the study or the well established principles of dose response.

Data on dose response are important since, from a practical point of view, it is generally impossible to meaningfully test enough animals at the lower levels of societal concern in a rodent bioassay. Therefore, we have to rely on data obtained in laboratory animals at higher dose levels and extrapolate from that data to the lower levels of human consumption. Now a dose response curve can have a number of shapes. Two hypothetical shapes are shown below:





In the first case, the tumor response data obtained in the laboratory animals indicate that the curve has a shallow slope and that a continuation or extrapolation of that curve predicts an increase in response at the lower levels of human use. In the second curve, which is similar to the curve generated by the data from the IRDC NaS study, the dose response is very steep indicating that the response drops off rapidly with dose and no response would be expected at the lower levels of human use. Various risk extrapolation models can be fitted to the laboratory animals data and, depending on which model is selected, very different estimates of risk will be obtained. However, regardless of which model is used, the estimates of risk will be lower and the confidence limits much smaller using the data from the IRDC NaS study versus the estimates of risk made in 1977 by the National Academy of Sciences using the pre IRDC data base. These estimates using the data from the IRDC NaS study range from zero using the threshold model to an increased risk of six in one hundred thousand using the most conservative model which fits the data in a statistical sense, i.e. multistage model with a linear term. In addition, while the selection of a risk extrapolation model is rather arbitrary, the shape of the dose response curve for NaS and the strong correllation between the physiological changes and the occurrence of tumors strongly argue in favor of using a threshold model or at least some model without a linear term which, in essence, assumes that one molecule of NaS could cause a bladder tumor. In this regard it is important to note that the dose response data from the IRDC NaS study overwhelming rejects the one-hit model which was the risk extrapolation model of choice used by the regulatory agencies when the IRDC NaS study was being designed. While the data from the IRDC NaS study cannot reject the multistage model with a linear term in a statistical sense, the latter risk extrapolation model predicts the same increased bladder tumor incidence as that predicted by the rejected one hit model. This provides further support for the argument that the multistage model with a linear term is not an appropriate model for NaS.

All of the primary objectives of the IRDC NaS study were accomplished. A well defined dose response for bladder tumors was obtained. This dose response was very steep, indicating that the tumor response drops off very rapidly with a decrease in dose. Secondly, the tumor response was strongly correlated with the occurrence of physiological changes, especially changes in urinary physiology. For example, among the animals for which urinalysis data were collected, one could predict with a very high degree of confidence which animals would develop bladder tumors based upon urinalysis data collected during the first few months of the study. With regard to the objective of evaluating the role of in utero exposure it was demonstrated that in utero exposure plays little or no role in the occurrence of the bladder tumors.

Probably one of the most discussed points concerning the IRDC NaS study has been the no-effect level for bladder neoplasia. This is unfortunate because defining a no-effect level in the same terms as it is used in traditional carcinogenicity bioassays was not one of the purposes of the study. The reason that it wasn't is because the term no-effect level defined in this manner is an arbitrary level where no response (or no significant response different from the control) is observed. It doesn't mean that no-effect will occur at that level, only that no-effect was observed in a given experiment. In traditional carcinogenicity studies it is generally established with a group of 50 animals. In the case of the IRDC NaS study, one doesn't have to rely on the results obtained in 50 animals or even in 700 animals to define the no-effect level. One can use the data from all 2150 animals used in the dose response portion of the bioassay to define the no-effect level and do so with a high degree of confidence. These data, when "plugged into" the threshold model (the only risk extrapolation model that assumes a threshold or no-effect level), show that the no-effect level isn't 1.0% but 2.83%. It can also be unequivocably stated that by all other traditional methods of defining a no-effect level, the 1.0% dietary concentration in the NaS IRDC is a no-effect level for bladder neoplasia. The first method that is usually used to define the no-effect level is statistical analyses of the data for either an increase in incidence of tumors or a decrease in time to observation of tumors. No matter how the data in the 1% level were statistically analyzed, no statistically significant (P=0.05) increase in tumors was observed. Another procedure frequently used in carcinogenicity studies to determine if there is a biologically significant increase in tumor incidence at a given level is to compare the tumor data from the study in question with the background or historical control data for that tumor in the same strain of rat. This exercise utilizing the control data from 10 other similarly conducted studies showed that the background incidence for bladder tumors at IRDC was 0.8% or exactly the same as the tumor incidence at the 1.0% dietary concentration in the IRDC NaS study. A third option which is occasionally used to determine if a bladder tumor incidence represents a real increase over the control is to have the tissues reexamined microscopically by another pathologist. This exercise was also conducted by the sponsor of the IRDC NaS study. This reexamination was conducted by Dr. Robert Squire, a well known and respected pathologist. Dr. Squire examined the tissues in a blind fashion, i.e. without knowledge of treatment groups, using his standard criteria for grading all lesions. The results of Dr. Squire's examination again demonstrated that there was no difference in the bladder tumor incidence between the control and 1.0% NaS treatment group. Dr. Squire's examination even raised questions as to whether or not the 3% NaS treatment group was an effect level for bladder neoplasia. Therefore, whether one wants to determine the no-effect level by statistical methods using all of the data obtained in the study or by other traditional methods, the 1% dietary concentration in the IRDC NaS study is a no-effect level for bladder neoplasia in male rats. The fact that this can be stated in such an unequivocal manner is a big improvement over the situation which existed before the IRDC study was conducted. Prior to the IRDC study, the no-effect level of 1.0% was based on data from 22 rats. It was rewarding to see in a recent review of the IRDC data by the Joint Expert Committee on Food Additives that they considered the 1.0% NaS dietary concentration as the no-effect level for calculating the acceptable daily intake (ADI).

The main point I hope I have made in this testimony is that the IRDC NaS study has made a large contribution to the overall understanding of NaS's potential hazard to human beings. The steep and well defined dose response and the demonstration that the bladder tumors are highly correlated with other changes in physiology (especially urinary physiology) should provide assurrance to anyone reviewing the data from the study that it is consistent with the overall findings of the large NCl epidemiology study conducted by the National Cancer Institute and that it is extremely unlikely that the increase in bladder tumors observed at high dose levels in male rats would occur in human beings at normal levels of human consumption.

The **Chairman**. Thank you, Dr. Schoenig.

Let me just ask you a few short questions and then turn to Senator Metzenbaum.

What was your role in the IRDC study?

Dr. **Schoenig**. My role in the study was study monitor. I was hired by the sponsor of the study to assist in the design of the study and then to serve as an independent monitor between the sponsor and the laboratory itself.

The **Chairman**. In your opinion, does the IRDC study provide any evidence that saccharin is a real danger to human beings?

Dr. **Schoenig**. Well, I feel that it provides exactly the opposite, because, in contrast to the situation in 1977 when we had essentially three points representing some tumor response at 5 percent and/or 7.5 percent, now we have a well defined dose response curve that shows that the dose response is very steep, and even at 1 percent, which is still a very high dose, there was no statistically significant increase in tumors.

If we were to have found another dose response curve that was very shallow and indicated that there may be some response at doses below 1 percent, then one would think that there may be some risk.

The other thing we were able to show in this study is a very strong correlation between physiological changes with the occurrence of tumors. When we did not see physiological changes, we did not see tumors.

The **Chairman**. I see. Are you familiar with the results of the NCTR study?

Dr. **Schoenig**. Yes, I am.

The **Chairman**. What do you think of it? Do you have any comment that you would care to make on it?

Dr. **Schoenig**. Well, I would like to add a couple of comments to that.

The **Chairman**. All right.

Dr. **Schoenig**. This is the study whose results are up on the board. I think it is important to consider just a few things when looking at that study.

First of all, the model that is used in this particular study really lacks applicability to a human situation. I am not sure whether or not you are familiar with the procedure which is used to dose these animals, Senator Metzenbaum, but what is done with these animals when they use MNU as an initiator, is not they actually take this very potent carcinogen, bladder carcinogen, and instill it directly into the bladder.

This material is not only a potent bladder carcinogen, but it is also very cytotoxic, so the epithelium of the bladder is in a very compromised state to begin with. So the model itself kind of lacks applicability to any type of human situation.

The second thing, with regard to results of the study, is, as Dr. Hart mentioned, ideally, what you want to do with an initiator is to give a dose of initiator where you don't see very much of a tumor response. In this study, they saw a rather high tumor response just with MNU.

The second thing the study was designed for was a dose response. As you can see, even though Dr. Hart did not mention it, way out there at the end is the 5-percent level, and there is no response there. At the highest dose level in this study, they had no increase in tumors.

So it is very hard to interpret what might be going on at 0.10 percent or 0.5 percent or 0.2 percent when you don't have any effect at your highest dose. It is like saying the more you give, the fewer tumors you see. That clouds the ability to really interpret or get any meaning from the study. I just thought I would add those couple of comments.

The CHAIRMAN. Now, if I understand correctly, your study showed an effect at a dose in rats of 3 percent saccharin.

Dr. SCHOENIG. That is correct.

The CHAIRMAN. But it showed no effect at 1 percent. Is that correct?

Dr. SCHOENIG. That is right. By all traditional methods of evaluating a no-effect level, 1 percent is a no-effect level in this study.

The CHAIRMAN. Now, how do these dose levels translate into terms of human consumption of saccharin?

Dr. SCHOENIG. Well, 1 percent would be equivalent to 250 cans of saccharin-sweetened beverages, totally saccharin, and the 3 percent would be 750 cans.

The CHAIRMAN. Is that per day?

Dr. SCHOENIG. Per day.

The CHAIRMAN. So if you are talking about 1 percent, you are talking about 250 cans of Diet Coke a day.

Dr. SCHOENIG. Sweetened entirely with saccharin.

The CHAIRMAN. Or whatever it is, if it is sweetened entirely with saccharin. I guess it is not fair to mention any particular product because they all sometimes use different things. But 250 cans of some sweetened carbonated beverage per day.

Dr. SCHOENIG. That is correct.

The CHAIRMAN. And 750 if you take the 3 percent.

Dr. SCHOENIG. That is correct.

The CHAIRMAN. Senator Metzenbaum?

Senator METZENBAUM. Dr. Schoenig, you are from where?

Dr. SCHOENIG. I am from Annapolis, MD.

Senator METZENBAUM. And what do you do in Annapolis?

Dr. SCHOENIG. Well, I am an independent toxicology consultant, and my office has been located in Annapolis for the last 6 years.

Senator METZENBAUM. And you were hired by the sponsors of this study to sort of supervise it and put it together. Was that it?

Dr. SCHOENIG. Right. I was hired by them initially to help them in the design of the study. They had a statistician and me and a few company toxicologists, and we worked on the design of the study.

Senator METZENBAUM. Who were the sponsors?

Dr. SCHOENIG. The sponsor was the Calorie Control Council, which is trade——

Senator METZENBAUM. The what?

Dr. SCHOENIG. The Calorie Control Council, which is a trade association.

Senator METZENBAUM. A trade association of those who deal in these products. It is really the industry.

Dr. SCHOENIG. In dietetic foods, yes.

Senator METZENBAUM. The industry. Would you say that is correct?

Dr. SCHOENIG. That is correct.

Senator METZENBAUM. And is it fair to say that you are generally known as an industry toxicologist?

Dr. SCHOENIG. I guess that would have to be the case, yes.

Senator METZENBAUM. And is it true that this study set out to prove that a no-effect dose exists for saccharin; that is, that there is a dose level at which you fail to detect increased incidences of bladder cancer in the rat?

Dr. SCHOENIG. No, that is entirely incorrect. We set out to determine what the dose response was. Actually, if I might just add one statement, Senator Metzenbaum, if you have a toxicology study where you have a defined dose response, the no-effect level defined in traditional terms really is not even a useful item, because the no-effect level is a rather ambiguous term which is only used when you cannot define the dose response. Once you have a dose response, the no-effect level, from a statistical point of view or from a health hazard point of view, is not even a useful item.

It is really unfortunate there has been so much discussion about the no-effect level, whether it is one percent or not, because it really doesn't make any difference.

Senator METZENBAUM. The FDA, in an internal document which I am sure you have seen, because we have seen it, says that the present study has once again confirmed that saccharin is a bladder carcinogen in the male rat. Do you agree with that?

Dr. SCHOENIG. I say that it produces tumors in the male rat. I would not call it a carcinogen.

Senator METZENBAUM. And you indicated——

Dr. SCHOENIG. For example, you can implant a glass bead in a rodent bladder and you will get a tumor. I would not call a glass bead a carcinogen. I think that we are talking about the same type of thing here. You are disrupting the physiology of the bladder and, therefore, you are making it more susceptible to the occurrence of a tumor.

Senator METZENBAUM. Dr. Schoenig, is it not the fact that almost all of the other studies, some in greater degree and some in lesser degree, have concluded that saccharin in rats is a carcinogen, produces carcinogens?

Dr. SCHOENIG. The conclusion has been that it produces tumors. Now, some people call everything that is a tumor a carcinogen. I don't call it that, and most toxicologists today make a distinction between a compound that is a carcinogen and a compound that produces tumors.

Senator METZENBAUM. Explain for us the difference.

Dr. SCHOENIG. OK. A compound that I would call a carcinogen is a compound that can enter the body and interact with the genetic material of the cell, cause a mutation and, therefore, cause a cancer cell. Then that cells goes on and proliferates and expresses itself.

You can go to the other extreme and use the example that I just used of a glass bead, where you can implant that in the bladder. I don't know even the mechanism of how a glass bead produces a tumor, but I could not call that a carcinogen. I would call that something that is acting indirectly.

In other words, the key thing is, the glass bead itself is not producing the tumor. It is doing something in between there. Something happens in between the implanting of the glass bead and the occurrence of a tumor, and that kind of compound I call an oncogen, or that kind of material, and the other one where I know it is reacting with the genetic material of the cell, I know it can cause mutations in the test tube or in the body, I would call a carcinogen.

Senator **METZENBAUM**. Now, the Department of Health and Human Services, on August 1, 1984, in connection with this particular study, indicated the Calorie Control Council submitted new data on the dose response of saccharin-induced bladder cancer in male Sprague Dawley rats.

As I look at that and read what they say about it—I did not read the report, but let me ask you whether they are just lying. Their conclusion is: The findings of the IRDC study support the following observations: One, the dose response for saccharin-induced bladder cancer has been shown to extend from 7.5 percent to 1 percent saccharin in the diet of male Sprague Dawley rats.

Now, they talk, A, about cancer; and, B, they talk about 1 percent. Are they just poor readers and didn't understand your report, or are you leading us astray? I don't know whom to believe, but you submitted it to them.

Their conclusions were—this was the Cancer Assessment Committee of the FDA, and you come here and you testify that 1 percent up to about 3 percent, there really isn't that much impact. Here they say that they read your report and it is from 7.5 to 1 percent, and they also say that it is cancer-producing, and you want to use the word "tumor." I am not sure whether you are not giving me a snow job from the industry component.

Dr. **SCHOENIG**. I can assure you that I am not giving you a snow job. Dr. Young started to address that very question when he said that that was the dose, the range of doses that we looked at, and then Dr. Gary Flamm—just like I am going to say the same thing to you—there was not a statistically significant increase at 1 percent; it was at 3 percent and above.

Senator **METZENBAUM**. Wait 1 minute. He said there wasn't a statistically—he did indeed say there was. He said that you would have——

Dr. **SCHOENIG**. Not at 1 percent.

The **CHAIRMAN**. He said there was an increase, but it was not statistically significant. Is that right?

Senator **METZENBAUM**. OK; but he said there was an increase, that you might have a couple of people if you didn't give them saccharin, but you would have maybe five people—rats—out of the 700 if you gave them the saccharin.

Now, I suppose that it isn't relevant unless you happen to be the rat.

Dr. **SCHOENIG**. No; it would be relevant if it were me. Then when you got into the discussion with Dr. Flamm about the background tumor incidence, he said that he would expect two or three.

Now, we went back and looked at the background tumor incidence in this laboratory, in studies that were run essentially concurrently with the IRDC study, and we found out the background tumor incidence was 0.8 percent. That is exactly the tumor incidence in our 1-percent group, 0.8 percent. They are identical. The background tumor at that laboratory and at 1 percent are identical.

Senator **METZENBAUM**. Well, as a matter of fact, isn't it the case that the FDA wanted you to use 1,000 rats, or suggested that it would be statistically significant if you used 1,000 rats, but somehow you were only willing to use 700? What about that question? Was there some shortage of funds for the extra 300 rats?

Dr. **SCHOENIG**. No; I don't believe there was any shortage of funds, and I don't remember any discussion with the FDA that we should have used 1,000 rats.

The **CHAIRMAN**. There is certainly no shortage of rats, is there? [Laughter.]

Dr. **SCHOENIG**. There was no shortage of rats.

Senator **METZENBAUM**. Let me read you what they say.

Dr. **SCHOENIG**. All right.

Senator **METZENBAUM**. From an internal FDA document reviewing the IRDC study:

> At this dose, over 1,000 animals would have had to be used to statistically detect the incidence of tumors predicted. Nevertheless, the study sponsors were unwilling to assign this many animals to the one percent dose level and chose 700 as an acceptable number.
>
> This severely weakens the statistical sensitivity of the one percent group and precludes the sponsor from being able to state this as a no-effect dose, as a statistically nonsignificant response is obtained.

So, I guess, really, they did seem to think that 1,000 would be preferable, but that you were unwilling to assign that many animals to the 1-percent dose level.

Dr. **SCHOENIG**. No; that is not a correct interpretation. It sounds like that was a review after the study was completed. In the study protocol itself, before the study was conducted, we discussed the number of animals that were placed at the 1-percent level. We did have a limit on the total number of animals, the 2,500 that we could get in the study room, because we wanted to do the whole study in one room.

Seven hundred was picked simply because, according to our statistician, we would have needed over 1,000—not 1,000 but over 1,000—to detect a statistically significant increase. Our very study protocol states that before one animal was ever put on test, it states right in there that the 1-percent level does not have the same statistical power as the 3 percent and above, and it is stated right in there that we knew that that was the case before, and FDA reviewed our protocol before we started the study, and there was never any recommendation to put 1,000 or more animals before the study started.

Senator **METZENBAUM**. I am glad the industry was not sticky about another 300 rats. [Laughter.]

Thank you, Mr. **CHAIRMAN**.

The **CHAIRMAN**. Thank you, Dr. Schoenig.

Dr. **SCHOENIG**. Thank you.

The **CHAIRMAN**. Now, if you need to leave, we will be happy to excuse you as well. We appreciate the testimony.

Dr. Arnold, welcome to the United States. We appreciate our neighbors to the north, and we appreciate your being here, and I am sorry that this has taken so long, because we know that you need to get back to your country. Let's turn to you at this point.

STATEMENT OF DOUGLAS ARNOLD, PH.D., RESEARCH SCIENTIST, HEALTH PROTECTION BRANCH, HEALTH AND WELFARE CANADA

Mr. **ARNOLD**. Thank you, Chairman Hatch and Senator Metzenbaum. Just one minor correction, Senator. I am an American working for the Canadian Government, so I am coming back home, so to speak.

Senator **METZENBAUM**. You are an American who works for the Canadian Government?

Mr. **ARNOLD**. Yes, sir.

The **CHAIRMAN**. Well, then, we are happy to welcome you back to your country. [Laughter.]

Senator **METZENBAUM**. Are you an Ohioan, too? [Laughter.]

Mr. **ARNOLD**. No; I am from Massachusetts. I am sorry that Senator Kennedy could not be amongst us today.

I was asked to prepare a statement in two parts, one part deals with my involvement with saccharin from the time that I joined the Health Protection Branch in 1976. I was immediately named study director for the ongoing Health Protection Branch two-generation saccharin feeding study, and we subsequently——

Senator **METZENBAUM**. You are a little hard to understand. Slow it down a little and pull that mike a little closer, will you?

Mr. **ARNOLD**. I am sorry, Senator.

Senator **METZENBAUM**. Thank you.

Mr. **ARNOLD**. My statement is in two parts, one dealing with my experience in regard to involvement with saccharin. When I joined the Health Protection Branch in 1976, I became study director for what is known as the Health Protection Branch two-generation saccharin study.

We subsequently did some additional work into the potential mechanisms by which saccharin may possibly be producing bladder tumors in Sprague Dawley rats, which led into a series of dead ends; so we abandoned that particular line of research. For the intervening years, I have chronologically listed various articles which I have authored or coauthored or presentations I have made to professional societies regarding saccharin.

Regarding the second portion of my written statement, it concerns the Canadian position on saccharin. On March 9, 1977, as you are well aware, the Minister of Health and Welfare of Canada announced that after careful evaluation of the scientific evidence, he would be banning saccharin as an additive to foods, drugs, and various cosmetic products.

He also concurrently announced that there would be a phaseout period for these products over the next several months, depending on the particular product and its use. In addition, the sale of saccharin as a single-ingredient drug or in combination with cyclamates would be limited to pharmacies as of September 1, 1977, to provide diabetics and others who must restrict their intake of carbohydrates with access to a carbohydrate-free sweetening agent.

Subsequently, in April 1977, the Minister announced a short extension in some of these phaseout dates for the various products containing saccharin.

In January 1978, an information letter was sent to industry which, in addition to reiterating the regulations which the Minister's announcement made necessary, also recommended that any——

Senator **Metzenbaum**. Dr. Arnold?

Mr. **Arnold**. Yes, sir?

Senator **Metzenbaum**. Why don't you try to just skip over some of the details and move into the thrust of what this committee's concerns are, because the chairman indicated he is short on time, a little more short on time than I am, but I think——

Mr. **Arnold**. What I was trying to emphasize, Senator, is the fact that Canada had a phaseout period for products containing saccharin. Saccharin was made available for sale in drugstores and Canada also required labeling on products containing saccharin, and essentially that was the gist of my statement.

In addition, none of the information, whether it had to do with animal studies, in vitro studies, or epidemiology studies, which have been conducted and reported in the intervening years, have brought a response from the Minister in regard to a reevaluation of the initial position announced in 1977.

[The prepared statement of Dr. Arnold and responses to Senator Grassley's questions follow:]

Statement of Douglas L. Arnold, Ph.D., Research Scientist, Health Protection Branch, Health and Welfare Canada. Pertaining to personal involvement with saccharin and the Canadian position regarding saccharin.

1974 Massachusetts Institute of Technology
Ph.D. in Nutritional Biochemistry and Metabolism

Major: Toxicology
Minor: Pharmacology

1976 Accepted a position with Health and Welfare Canada.
Named Study Director for the Health Protection Branch (HPB) two-generation feeding study initiated in 1974 to ascertain the carcinogenic potential of: 1) orthotoluenesulphonamide (the major impurity in Remsen-Fahlberg synthesized saccharin); and 2) a high dose of Maumee synthesized saccharin.

1977 Society of Toxicology: Long term toxicity with orthotoluenesulfonamide and saccharin. D.L. Arnold, S.M. Charbonneau, C.A. Moodie, & I.C. Munro, March 29, 1977, Toronto, Ontario. Toxicol. Appl. Pharmacol. 41: 164, abstract No. 78.

Joint University of Arkansas Medical School - U.S. National Center for Toxicology Research Urinary Bladder Workshop. Benign and malignant urinary tract tumors of rats induced by saccharin. C.A. Moodie, D.L. Arnold, B. Stavric, & I.C. Munro. May 25, 1977, Jefferson, Arkansas.

Champlain Section of the Society for Experimental Biology and Medicine. Long term toxicity of orthotoluenesulphonamide and saccharin in the rat. D.L. Arnold, C.A. Moodie, H.C. Grice, S.M. Charbonneau, B. Stavric, & I.C. Munro. May 28, 1977, Ottawa, Ontario.

Annual meeting of the Canadian Congress of Laboratory Medicine. Benign and malignant urinary tract tumors of rats induced by saccharin. D.L. Arnold, C.A. Moodie, & B. Stavric. June 25-29, 1977, Hamilton, Ontario.

25th Annual Meeting of the American Society of Cytology. Cytological detection of bladder tumors of rats fed saccharin. C.A. Moodie, D.L. Arnold, & B. Stavric. June 29, 1977, Hamilton, Ontario.

Letter to Editor: Canadian saccharin study. D.L. Arnold, C.A. Moodie, B. Stavric, D.R. Stoltz, H.C. Grice, & I.C. Munro. Science 197: 320, 1977.

Medical Tribune, Internationale Wochenzeitunq - Ausgabe für Deutschland. Glaubenskrieg um Saccharin. D.L. Arnold, July 11, 1977.

Toxicology Forum - World Health Organization Workshop: "Long term toxicity of orthotoluenesulfonamide and saccharin in the rat". D.L. Arnold, C.A. Moodie, H.C. Grice, S.M. Charbonneau, & I.C. Munro. April 15, 1977, Geneva, Switzerland.

Toxicology Forum: "Long term toxicity of orthotoluenesulphonamide and saccharin in the Rat". D.L. Arnold, C.A. Moodie, H.C. Grice, S.M. Charbonneau, B. Stavric, & I.C. Munro. May 10, 1977, Omaha, Nebraska. Proceedings: Saccharin, pp 81-94, Toxicology Forum, 1977.

University of Toronto, Department of Nutrition and Food Science, Faculty of Medicine. "Saccharin: The controversial sweetener". D.L. Arnold. October 3, 1977.

Ottawa Biological and Biochemical Society. "Saccharin: Issues and uncertainties". D.L. Arnold. November 16, 1977. Ottawa, Ontario.

Canadian Association for Research in Toxicology; Symposium on Nutrition, Food Additives and Toxicity. "Artificial sweetening agents: Current status". D.L. Arnold. December 6 and 7, 1977, Montréal, Québec.

1978 Toxicology Forum: "The urinary effects of saccharin and other salts". D.L. Arnold, P.F. McGuire, E.H. Nagy, D.A. Beck, & I.C. Munro. July 23, 1978, Given Institute, Aspen, Colorado. Proceedings: Saccharin Update, Special Session, pp 67-72, Toxicology Forum, 1978.

European Research Group for Oral Biology. "Chronic Bioassay Review" (concerning saccharin studies only). I.C. Munro & D.L. Arnold. October 30 - November 1, 1978, Geneva, Switzerland; in Health and Sugar Substitutes (Proceedings of the ERGOB Conference on Sugar Substitutes; pp. 76-81, Ed. B. Guggenheim, 1979, ISBN 3-8055-2961-9, S. Kager.

U.S. National Center for Toxicological Research. "Saccharin: Its Ironic Past and Present Research". D.L. Arnold. November 20, 1978, Jefferson, Arkansas.

1979 The effect of orthotoluenesulphonamide and sodium saccharin on the urinary tract of neonatal rats. D.L. Arnold, C.A. Moodie, P.F. McGuire, B.T. Collins, S.M. Charbonneau, & I.C. Munro. Toxicol. Appl. Pharmacol. 51: 455-463, 1979.

A look at saccharin. D.L. Arnold, I.C. Munro, & H.C. Grice. International Register of Potentially Toxic Chemicals 2: 11-13, 1979.

1980 Toxicology Forum: The effect of sodium on several urinary constituents of the rat and the statistical evaluation thereof. D.L. Arnold, July 27, 1980, Aspen, Colorado. Proceedings: Saccharin Working Group of the Toxicology Forum, pp. 71-86, Toxicology Forum, 1980.

Long term toxicity of orthotoluenesulphonamide and sodium saccharin in the rat. D.L. Arnold, C.A. Moodie, H.C. Grice, S.M. Charbonneau, B. Stavric, B.T. Collins, Z.Z. Zawidzka, & I.C. Munro. Toxicol. Appl. Pharmacol. 52: 113-152, 1980.

Society of Toxicology: The effect of sodium saccharin on several urinary parameters in the rat. D.L. Arnold, B. Stavric, P.F. McGuire, & I.C. Munro. March, 1980. Abstract No. 228.

Canadian Federation of Biological Societies. Urinary and serum proteins in mature non-treated and saccharin-fed rats. B. Stavric, H. Tryphonas, D. Beck, P.F. McGuire, E. Nagy, R. Klassen, M.G. Bickis, & D.L. Arnold. June 10-13, 1980, St. John's, Newfoundland. CFBS Programme and Proceedings 23: 123, Abstract No. 433.

1981 The two-generation saccharin bioassays. D.L. Arnold. Proceedings of the International Symposium on Health Effects of Tumor Promotion, Oct. 12-15, 1981. Environ. Health Perspect. 50: 27-36, 1983.

1982 A Century of Saccharin. L. Bradshaw, D.L. Arnold, & D.R. Krewski; in: Living with Risks: Environmental Risk Management in Canada, pp. 117-128, eds. I. Burton, C.D. Fowle, & R.S. McCullough. General Editor R.E. Munn. Environmental Monograph No. 3. Inst. for Environmental Studies, Univ. of Toronto, 1982, Publication No. EM-3.

Joint Meeting of the American Society of Pharmacology and Experimental Therapeutic and the Society of Toxicology. Symposium on Current Concerns in Environmental Pharmacology and Toxicology. Toxicology of saccharin. D.L. Arnold, August 15-19, 1982.

1983 Artificial Sweeteners; Their Toxicological Etiology is an Interesting Mix. D.L. Arnold & I.C. Munro. In: Environmental Aspects of Cancer: The Role of Macro and Micro Components of Foods, pp. 211-229. Eds, E. Wynder, G.A. Leveille, J.H. Weisburger & G.E. Livingston, 1983, ISBN 0-917678-17-6, Food and Nutrition Press, Inc.

Saccharin: A historical and toxicological perspective. D.L. Arnold, D.R. Krewski, & I.C. Munro. Toxicol. 27: 179-256, 1983.

1984 Toxicology of saccharin. D.L. Arnold. Fund. Appl. Toxicol. 4: 674-685, 1984.

1985 Saccharin: A Bitter-Sweet Case. D.L. Arnold & D.B. Clayson. To appear in Toxicology Risk Assessment (Eds. D.B. Clayson, D.R. Krewski, & I.C. Munro). CRC Press. (accepted for publication).

Case studies - Saccharin: Still a controversial sweetener. D.L. Arnold and D.R. Krewski. To appear in Information Needs for Environmental Risk Management in Canada, ed. T. Mann (in preparation).

THE CANADIAN POSITION ON SACCHARIN

Health Protection Branch
Health and Welfare Canada
(March, 1985)

On March 9, 1977 the Minister of Health and Welfare Canada announced that following careful evaluation of all the scientific evidence, and after consultation with experts from other countries, the artificial sweetener saccharin would be banned from use in foods, cosmetics and as a sweetening agent in drug preparations. A phase out schedule for these products was established, taking into account the amount of saccharin normally consumed in each product category:

1. The sale of soft drinks, beverage bases and beverage mixes containing saccharin would not be permitted after July 1, 1977.
2. The sale of all other foods containing saccharin would not be permitted after November 1, 1977. However, in consultation with medical experts and the food industry, consideration would be given to proposals regarding special foods for diabetics.
3. The sale of drugs containing saccharin as a non-medicinal ingredient would not be permitted after December 31, 1978. However, in consultation with medical experts, consideration would be given to recommendations for the possible use of saccharin in life-saving drugs.

4. The sale of cosmetics containing saccharin, such as mouthwashes and toothpaste, would not be permitted after December 31, 1979.
5. The sale of saccharin as a single ingredient drug or in combination with cyclamates would be limited to pharmacies as of September 1, 1977, to provide diabetics and others who must restrict their intake of carbohydrates with access to a carbohydrate-free sweetening agent.

On April 19, 1977 the Minister of Health and Welfare Canada announced that he had agreed to requests from Canadian food manufacturers for a short-term extension for the permitted sale of foods and beverages containing saccharin. The sale of soft drinks, beverage mixes and beverage bases containing saccharin would be extended to October 1, 1977 and for all other foods containing saccharin until December 31, 1977. The continued sale of saccharin alone or in combination with cyclamate was extended until February 1, 1978; after which it would be available in pharmacies as a non-prescription drug for use by diabetics and others who must restrict their intake of sugar.

These new dates took into account economic adjustment problems which could not have been foreseen when action to control saccharin was first announced. The soft drink industry encountered unforeseen difficulties in obtaining fructose syrup for reformulation of calorie-reduced soft drinks. In addition, this extension provided time for evaluation of new industry-sponsored data on the safety of alternative artificial sweeteners not permitted in food products at that time.

The Canadian Soft Drink Association provided assurances to the Federal Government that its members would not take advantage of the extension through promotional and advertising support for products containing saccharin.

In a January 18, 1978 Information Letter to Food, Drug and Cosmetic manufacturers, the Assistant Deputy Minister, Health Protection Branch, advised the industries as to regulations that would be recommended based on the above announcements. In addition to the various phase out dates listed above, it was also recommended that any sweetener containing saccharin or saccharin and cyclamate, would be required to carry a label statement to the effect that continued use of saccharin may be injurious to health and that it should not be used by pregnant women, except on a physician's advice. These labelling requirements became effective on January 1, 1979.

The initial announcement by the Minister of Health and Welfare Canada to ban saccharin from use in foods, cosmetics and as a sweetening agent in drug preparations was based to a large degree upon the following considerations.

1. Animal Studies: While a number of one-generation feeding studies, including one conducted at the Health Protection Branch, did not indicate any potential toxicological problems for humans ingesting saccharin, studies using the two-generation experimental model conducted at the Wisconsin Alumni Research Foundation (WARF) and the U.S. Food and Drug Administration (FDA) demonstrated a statistically increased incidence of bladder tumors (some benign and some malignant) in second generation male rats fed diets containing high dosages of Remsen-Fahlberg synthesized saccharin. Subsequent work by analytical chemists at the Health Protection Branch found the Remsen-Fahlberg synthesized saccharin contained a number of impurities, one of which, orthotoluenesulphonamide (o-TS), was hypothesized as possibly being the chemical responsible for the bladder tumors found in the two-generation rat feeding studies. Health Protection Branch scientists initiated a two-generation feeding study in 1974 to test this hypothesis as well as to evaluate whether a high dose of Maumee synthesized saccharin might elicit bladder

tumors in rats. The results of this study clearly demonstrated that saccharin, and not an impurity, was most likely responsible for the bladder tumors observed in the second generation males of all three, two-generation rat feeding studies.

2. Epidemiology Studies: Prior to the Minister's announcement, several epidemiological studies were available regarding possible relationships between artificial sweeteners and the incidence of bladder cancer in diabetic and non-diabetic populations. While none of these studies indicated any correlation between saccharin consumption and health problems, extrapolation of the animal study results indicated that the sample size of these epidemiological studies was too small to detect any possible correlation if saccharin had a similar potency to elicit bladder tumors in the human population as it did in the animal studies.

3. Benefits: The available literature did not contain any valid studies to support any of the purported benefits of saccharin usage. However, a genuine need by the diabetic population and those people who wished to control their carbohydrate consumption was acknowledged.

4. Commercial Sector Displacements: A balance between possible long-term adverse health effects in humans from the consumption of saccharin against the dislocation to the food and beverage industries and their employees brought about by any action to restrict saccharin use was taken into account.

In the intervening years, a number of animal, in vitro and epidemiological studies have been conducted. It has been concluded that none of these studies support any change to the present regulatory status of saccharin. However, the Health Protection Branch is continuing to review any new information as it becomes available and is prepared to reexamine its position in light of new data.

Answer to Senator Grassley's Question

Insofar as the NCI-FDA epidemiological study is concerned, the following observations have been made:

1. The use of dietary recall poses significant problems as it relies heavily on the individual's memory. This in turn will impact on the accuracy of the data related to artificial sweetener consumption.
2. A number of factors significantly reduced the size of the sample population (i.e. by ∿35%) thus weakening the data base upon which the conclusions were based (Ref: Progress Report to the FDA from the NCI concerning the National Bladder Cancer Study).
3. Statistical evaluation has indicated that this study had a low probability of detecting any effects of artificial sweeteners upon human health.

Thus, it is considered that the results of this study should be viewed cautiously.

Regarding the International Research & Development Corporation (IRDC) study, this study employed a number of dietary levels of saccharin ranging from 1% to 7.5%. It is generally agreed that there was a statistically significant increase of bladder tumors in male rats consuming >1% saccharin in their diet. Although the incidence of bladder tumors observed in the 1% treated group was not statistically significant, in the absence of any bladder tumors in the concurrent control group, this finding cannot be summarily dismissed. In addition, statistical evaluation has raised the question of "sensitivity" of this study to detect a definite toxicological effect at the 1% dose level. Therefore, the interpretation of this study as it relates to the establishment of a "NOEL" and subsequent extrapolation to man is questionable.

Bureau of Chemical Safety,
Food Directorate,
Health Protection Branch

July 24, 1985.

The CHAIRMAN. Senator Metzenbaum, we will turn to you. You go ahead and ask whatever questions you would like.

Senator METZENBAUM. Did you make a study in 1977 linking saccharin to rats in the laboratory?

Mr. ARNOLD. Upon conclusion of the two-generation feeding studies performed at WARF [Wisconsin Alumni Research Foundation], and at the Food and Drug Administration, which showed a correlation between saccharin ingestion and bladder tumors in male rats, versus the findings for the previous single-generation studies which showed no such correlation, scientists at the Health Protection Branch suggested that it was the major impurity in the Remsen-Fahlberg-produced saccharin—namely orthotoluenesulphonamide, or OTS, as it is commonly called—which was the culprit for producing the bladder tumors.

The major objective of our study was to ascertain whether that hypothesis was correct or incorrect. In addition, just prior to the start of that study, we obtained some Maumee-produced saccharin which does not contain OTS. We fed the Maumee-produced saccharin to one group of rats, which would be, we thought at the time, a negative control group.

Our conclusion from the study was that OTS was in no way associated with the production of bladder tumors in male Sprague Dawley rats and that saccharin was the culprit. If it was another impurity in the Remsen-Fahlberg-produced saccharin, that was responsible for the bladder tumors, this impurity also had to be found in the Maumee-produced saccharin. Such an impurity would have to be the most potent bladder carcinogen that man knows of.

Senator METZENBAUM. Dr. Arnold, tell me why you concluded and recommended, apparently, to the Canadian Government that they should ban the sale of saccharin; and American scientists, others testifying here today, indicate that the evidence is not complete enough. Why do you feel that the evidence is sufficiently complete to ban the sale of saccharin and to require people to get cyclamates? Is that what they can get by prescription in the drugstores?

Mr. ARNOLD. No; both saccharin and cyclamate are available over the counter in the drugstore to anybody that wants to go in and purchase them, Senator.

The Minister, after evaluating all the data regarding animal studies, epidemiology studies, purported benefits, and economic displacement in the commercial sector, concluded that it was prudent that saccharin be banned as a food additive, drug additive, and cosmetic additive.

Senator METZENBAUM. Do you consider saccharin to provide a health risk to humans?

Mr. ARNOLD. I think the evidence indicates that there is a potential there for a very weak risk, yes.

Senator METZENBAUM. For what?

Mr. ARNOLD. A very weak or small risk.

Senator METZENBAUM. A very small risk?

Mr. ARNOLD. Yes, sir.

Senator METZENBAUM. Do you or your children use saccharin or NutraSweet or cyclamates?

Mr. **Arnold**. No, none of my family uses saccharin, cyclamate, or aspartame, but I wouldn't say I am the average, typical North American father, because I have just gotten through training——

Senator **Metzenbaum**. What?

Mr. **Arnold**. I wouldn't consider myself an average North American father from the point of view that I have just been traning my son for a 10-kilometer road race. So, consequently, I am not concerned about his ingestion of calories, sir.

The **Chairman**. Let's come up with a better question here, Howard. I am worried you are bogging down a little. [Laughter.]

Senator **Metzenbaum**. The Calorie Control Council took out a full-page ad complaining that the dosage you gave those Canadian rats was more than a human would receive from drinking 1,250 diet sodas a day for a lifetime. How do you respond to that?

Mr. **Arnold**. Regarding the 1,800 or however many bottles of soda pop you want to call it, I think we have to go back and look at the philosophy of conducting toxicological tests.

I think there is wide agreement amongst toxicologists that the highest dose in any toxicological study must produce a response, a toxic response. Where the controversy comes in is how high should that quote, unquote, toxic dose be.

It has to be high enough for something like saccharin, which is relatively nontoxic—I am not trying to use that as a specific example per se, but essentially we are using a small population of animals which are acting as a surrogate for millions of people. We essentially are feeding this particular chemical to an animal for 2 years versus a potential lifetime exposure. And so, consequently, to increase the sensitivity due to these problems, toxicologists occassionally have to feed tremendously large doses relative to the amount that humans ingest.

This is a standard accepted practice. Where the problem comes in is the definition of the highest dose. It is oftentimes called the maximum tolerated dose. One definition is that of the maximum tolerated dose which is used by Dr. Sontag of the U.S. NCI; it is the dose which will not decrease the life expectancy of the animals on tests excepting due to tumors. Some other people would like to add an additional qualifier to indicate that it [MTD] should have no effect upon body weight or should at least not depress it to the point of a 10-percent or greater difference versus the concurrent control animals.

In all of the saccharin studies, there was a suppression at the 5-percent feeding level and above of body weight growth or body weight increase compared to the control groups of 10 percent or more. However, there was no decrease in the life expectancy of any of the saccharin-treated animals on any of the saccharin tests.

Senator **Metzenbaum**. If saccharin is a weak carcinogen—I think that is what you said——

Mr. **Arnold**. Yes, sir.

Senator **Metzenbaum** [continuing]. Why did you ban it? Does it pose any real threat to human health, or are we just kidding ourselves?

Mr. **Arnold**. Well, as I said, the Minister decided that it was prudent to take the course of action that he did.

Senator **Metzenbaum**. What do you think is prudent? Would you have done it?

Mr. **Arnold**. In view of the fact that there are no scientifically valid studies which show that there is a need for saccharin per se, and I believe there is a wish or a desire by the North American consumer to have a risk-free food supply, I believe that the decision was prudent.

Senator **Metzenbaum**. So you feel that to err on the side of caution is prudent?

Mr. **Arnold**. Particularly with a compound like saccharin for which there are no scientifically valid studies indicating there is a definite need. There is a perceived need, and the Canadian Government, or more correctly, the Minister of Health and Welfare addressed this aspect by having saccharin and cyclamate made available in the drugstore as an OTC [over the counter].

The philosophical aspect of this approach was that the insulin diabetic would be in the drugstore anyway picking up his insulin. Therefore, if they wanted saccharin or cyclamate, they could also pick it up at the same time. But it was a conscious decision on the part of the consumer to purchase it.

Not only could the diabetic purchase it, of course, but if it is available as an OTC, anybody that wanted to go into the drugstore could pick it up. But they had to go to the drugstore and, obviously, they were making a conscious decision to use that product for the perceived benefit that they felt they derived from it.

Senator **Metzenbaum**. Has there been any indicated problem from the diabetics by reason of the procedures that you follow?

Mr. **Arnold**. To the best of my knowledge, no, but I am a research scientist. I am not involved in the regulatory aspects of this situation. I do know of an insulin diabetic research scientist in my section that does not use artificial sweeteners in his control of his diabetic situation.

Senator **Metzenbaum**. He does control it?

Mr. **Arnold**. He does control his diabetic situation without the aid of artificial sweeteners.

Senator **Metzenbaum**. Dr. Arnold, you have heard some other witnesses testify today. As a scientist who has studied these questions for a good many years, if you had the final decision to make with respect to the sale of saccharin in this country, would you ban its use except through drugstores?

Mr. **Arnold**. Yes; I believe that it is prudent to remove it as a food and drug additive, except for drugs which may be needed, in life-threatening situations, to enhance their ingestion.

Senator **Metzenbaum**. Second, you have heard a number of scientists speak today. Do you care to offer any particular comment or to take issue or to indicate agreement with respect to the comments of any of them?

Mr. **Arnold**. Well, that could take the rest of the afternoon, Senator. I don't think I feel strong enough about any of the issues that have been brought up that I would particularly care to get into them at this time.

Senator **Metzenbaum**. And we do have for the record your background. What is your profession?

Mr. Arnold. I am a toxicologist. I graduated from MIT the year before they essentially put on that degree, but toxicology was my major. I majored in toxicology under Dr. Gerald Wogan's tutelate, who is the only toxicologist I am aware of that is a member of the U.S. National Academy of Sciences. I minored in pharmacology at B. U. Medical School.

Senator Metzenbaum. What was the name of that doctor? Was that Dr. Wurtman?

Mr. Arnold. Wogan.

Senator Metzenbaum. Not the Wurtman who is here?

Mr. Arnold. No. They are in the same department, but Wogan is essentially what I call the father of aflatoxin, which is a different problem.

Senator Metzenbaum. I thank you very much, doctor.

Mr. Arnold. Thank you, sir.

The Chairman. Dr. Arnold, let me just ask you one or two questions. What do the Canadians use in their soft drinks? I mean, what sweetener do they use for diet soft drinks?

Mr. Arnold. There was approximately a 2-year period in which——

The Chairman. No; answer what do they use now in their diet soft drinks?

Mr. Arnold. As of July 31, 1981, Senator, they use aspartame.

The Chairman. They use aspartame?

Mr. Arnold. Yes, sir.

The Chairman. What did they use before?

Mr. Arnold. There was nothing available. Some of the soda manufacturers provided unsweetened carbonated sodas which the individual could add their own sweetener to. Since saccharin and cyclamates were available over the counter, they went to the drug store and got their cyclamate or saccharin, and they self-sweetened it to their own satisfaction.

The Chairman. I see. So as of right now, the only sweetener is aspartame?

Mr. Arnold. The only one that can be used as a food additive, yes, sir.

The Chairman. But I take it saccharin is sold over the counter in the little sugar packs. Is that what you are talking about?

Mr. Arnold. Little sugar packs and also larger containers. Yes, sir.

The Chairman. I see. Is cyclamate——

Mr. Arnold. Cyclamate is available in the same manner, but I don't believe cyclamate is sold by itself. I believe it would be what is known in the trade as Sucaryl, which is the 10-to-1 mixture of cyclamate and saccharin.

The Chairman. Are cyclamates used as food additives?

Mr. Arnold. No, sir. It was removed the same time, in 1969, as when the U.S. Food and Drug Administration removed it.

The Chairman. I know that Senator Metzenbaum may have been construed to have asked the same question, but do you concur with the assessments of the IRDC and the NCTR studies that we have heard about from other panelists today?

Mr. Arnold. I think that Dr. Flamm indicated that the response at the 1-percent level in the IRDC study is where it gets potentially controversial. There are petitions submitted to regulatory agencies that when they don't see a particular incidence—that is, in the this case, bladder tumors—in the concurrent controls, they immediately like to look at the historical controls in an attempt to ameliorate the differences between the concurrent control and treated groups.

As was indicated, I believe, by Dr. Young, there are a lot of materials in commercial rodent diets which may act as a cocarcinogen or a promoter or this type of thing, and when you don't see bladder tumors, as in the IRDC study, in the concurrent control group, I would question whether historical controls are really relevant.

The historical controls may have been exposed to different dietary situations or different environmental situations which may have precipitated those tumors in the historical controls which, for whatever reason, unbeknownst to the researchers at the time, may not have been present at the time of the IRDC saccharin study.

So I think that what some scientists would suggest is that while there was not statistically increased incidence of bladder tumors in the 1 percent group of the IRDC study, there was a biological effect, because there were no incidences of bladder tumors in the controls.

The **Chairman**. Thank you. We appreciate your testimony, Dr. Arnold.

For our court reporter, we are going to take a 10-minute break and then recess for 10 minutes and be back at that time. We will start with our third panel, which will review the current science on aspartame.

We will hear from Dr. Frederick Trowbridge, Director of the Division of Nutrition at the Centers for Disease Control. Dr. Trowbridge will describe for us the results of CDC's extensive review of consumer complaints attempting to detect an causal link with aspartame.

Following him will be Dr. Richard Wurtman of MIT. Dr. Wurtman has raised questions concerning the behavioral effects of aspartame.

The final witness on this panel is Dr. Lewis Stegink, with the Department of Pediatrics and Biochemistry at the University of Iowa. Dr. Stegink is the coauthor of a book on aspartame and has a long history of research on the sweetener.

So, 10 minutes from now we will resume.

Senator **Metzenbaum**. Before you do that, may I ask Dr. Wurtman, does this comport with your time? Are you all right?

Dr. **Wurtman**. Yes.

Senator **Metzenbaum**. All right, fine. I knew you had to get away.

The **Chairman**. We will recess for 10 minutes and come back.

[Recess.]

The **Chairman**. I apologize for letting that 10 minutes slip, but the new nominee for Secretary of Labor was here to visit me. I felt that it was just something that I needed to do, of course, and I am happy to have been able to take that time. So I apologize for the delay. I hope we can finish within the next near few minutes.

We are very happy to have you here, Dr. Trowbridge. Dr. Wurtman, I am pleased to welcome you to the committee. And, of course, Dr. Stegink, we are very happy to have you here as well.

So we will begin with you, Dr. Trowbridge. We are going to limit you to 5 minutes apiece. We would like summaries. We are going to put your full statements in the record, and then we would like to have just a few questions and then go to the last panel.

Dr. Trowbridge.

STATEMENT OF FREDERICK TROWBRIDGE, M.D., DIRECTOR, DIVISION OF NUTRITION, CENTER FOR HEALTH PROMOTION AND EDUCATION, CENTERS FOR DISEASE CONTROL

Dr. **Trowbridge.** Mr. Chairman, I am Dr. Frederick Trowbridge, Director of the Division of Nutrition of the Center for Health Promotion and Education at CDC.

I am pleased to have this opportunity to review for you CDC's study for the Food and Drug Administration on the symptoms reported with aspartame use.

In February of 1984, FDA requested CDC's assistance in evaluating consumer complaints that FDA had received about the consumption of aspartame-containing products. The request followed an increase in aspartame-related complaints in the latter half of 1983. Complaints to the FDA increased from 108 in the first 6 months of 1983 to 248 in the last 6 months. This increase coincided with approval of aspartame for use in soft drinks in July 1983.

CDC agreed to provide a basic descriptive analysis of the symptoms reported and the epidemiologic characteristics of the persons reporting those symptoms and to determine whether specific individual symptoms or constellations of symptoms were reported with enough consistency to indicate where further clinical studies, should they seem necessary, would be most productive.

The major finding of our study—and if I could summarize: We studied some 517 cases which were reinterviewed after they had called FDA to register their complaint. We did an indepth study of some 231 of these cases. We found that in these cases, 96 percent of the complainants were white; 76 percent were female; and most were adults between the ages of 21 and 60 years.

We found from the records analyzed indepth that the most commonly reported specific symptoms were in the neurological behavioral category, including headaches, mood alterations, insomnia, dizziness, and fatigue. This group constituted 67 percent of the symptoms. Gastrointestinal symptoms were 24 percent of complaints, and allergic symptoms were 15 percent of complaints.

The major finding of our study was that no specific constellation of symptoms clearly related to aspartame consumption was identified. Despite great variety overall, the majority of frequently reported symptoms were mild and common in the general populace.

While some reports are undoubtedly due to the coincidence of symptoms and aspartame consumption, and others may be due to the suggestibility of some persons, still others may be attributable to some as yet undefined sensitivity of individuals to aspartame in commonly consumed amounts. The only way that these possibilities can be thoroughly evaluated would be through focused clinical studies.

In summary, currently available information based on the data with limitations that are described in the full text of my comments indicate a wide variety of complaints that were generally of a mild nature, although it may be that certain individuals have an unusual sensitivity to the product.

These data do not provide evidence for the existence of serious widespread adverse health consequences attendant to the use of aspartame.

Thank you.

[The prepared statement of Dr. Trowbridge follows:]

STATEMENT OF FREDERICK L. TROWBRIDGE, M.D.

CENTERS FOR DISEASE CONTROL
PUBLIC HEALTH SERVICE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Mr. Chairman and Members of the Committee, I am Dr. Frederick L. Trowbridge, Director, Division of Nutrition, Center for Health Promotion and Education of the Centers for Disease Control (CDC). I am pleased to have this opportunity to review for you CDC's study for the Food and Drug Administration (FDA) on the symptoms as reported with aspartame use.

In February 1984, FDA requested CDC's assistance in evaluating consumer complaints that FDA had received about consumption of aspartame-containing products. The request followed an increase in aspartame-related complaints in the latter half of 1983. Complaints to the FDA increased from 108 in the first 6 months of 1983 to 248 in the last 6 months. This increase coincided with approval of aspartame for use in soft drinks in July 1983.

CDC agreed to: (1) provide a basic descriptive analysis of the symptoms reported and the epidemiologic characteristics of the persons reporting those symptoms; and (2) determine whether specific individual symptoms or constellations of symptoms were reported with enough consistency to indicate where further clinical studies, should they seem necessary, would be most productive.

The major finding was that no specific constellation of symptoms clearly related to aspartame consumption was identified. Despite great variety overall, the majority of frequently reported symptoms were mild and are symptoms that are common in the general populace. While some reports are undoubtedly due to the coincidence of symptoms and aspartame consumption, and others may be due to the suggestibility of some persons, still, others may be attributable to some as yet undefined sensitivity of some individuals to aspartame in commonly consumed amounts. The only way these possibilities can be thoroughly evaluated would be through focused clinical studies.

It was recognized from the outset that this investigation alone would be unlikely to establish any cause-and-effect relationship between the ingestion of aspartame and the occurrence of reported symptoms. The data which provided the basis for this report were obtained from FDA's ongoing passive surveillance system. The quality and type of evidence that may be obtained by a passive surveillance system do not allow definitive determination of whether given symptoms are or are not caused by the agent under question. Passive surveillance in this instance implies that cases or reports are not actively solicited by the agency or organization concerned but, rather, are initiated on the part of the consumer or complainant. In such a passive surveillance system, serious problems may be more likely to be reported, even if they occur less often than mild problems. Problems occurring soon after use of a product are more likely to be thought to be caused by the product and, hence, reported. Thus, passive surveillance systems are more likely to detect rare and serious conditions and symptoms occurring shortly after use of a product than common symptoms or symptoms occurring at some longer period after product use. However, symptoms that are common in the general populace and are reported in a passive surveillance system are more likely to have occurred by chance in association with use of the product than are symptoms that occur more rarely.

To evaluate the likelihood that symptoms reported by individuals through this passive surveillance system could be due to aspartame consumption, we adapted criteria originally developed to assess potential adverse reactions to medications. However, application of these criteria was limited by a number of factors. For example, when evaluating reactions to medications, physician reports indicating concurrent illness and use of other medications are usually available. In the case of aspartame use, because few of the complainants sought medical aid, few physician reports containing information specific to the aspartame complaints were available. For this reason, information about other potential causes of symptoms, such as concurrent illnesses or medications, was often limited. Moreover, details relating to the time between ingestion of aspartame and onset of symptoms often were incomplete because aspartame consumption was part of the daily routine.

From the clinical studies performed before FDA approval of aspartame, there was little to suggest that acute reactions would be likely to occur. Therefore, no pre-defined symptom constellation could be specifically sought in reinterviewing complainants. As far as is known, complaints, such as those reported in this analysis as being associated with aspartame use, have not been commonly reported in other countries in which aspartame is also in use.

An important criterion in assessing potential adverse reactions is the consistency of reported symptoms with rechallenge, i.e., the recurrence of symptoms after consuming aspartame-containing products a second time. However, even the application of this criterion had substantial limitations.

People who experience symptoms once may be primed to experience them on repeated use. Conversely, persons with particularly serious or unpleasant complaints would be unlikely to use aspartame again, and, therefore, there would be no information on the effects of rechallenge.

Evaluation of dose-response relationships might have been fruitful had individuals reported symptoms with increasingly high consumption of aspartame-containing products. However, due to the difficulties in quantifying intake from the available data, evaluation of dose-response relationships was not possible.

Given these limitations inherent in passive surveillance systems, the lack of medical information, and the inability to fully apply the methods used to assess reaction to medications, I will now describe how we carried out the investigation. First, attempts were made to interview in depth all complainants who had reported problems before mid-April 1984 to the FDA; to G. D. Searle and Company, the manufacturer of aspartame; to the Arizona Department of Health Services; to Dr. Woodrow C. Monte, Director, Food Science and Nutrition Laboratory, Arizona State University; and to Mr. James C. Turner, Counselor, Community Nutrition Institute, Washington, D.C. Of 592 complaints received by these combined sources, we were able to obtain reports of interviews from 517 (87%).

By June 15, 1984, the date on which the CDC analysis began, 231 (45%) of the interviews had been completely coded and reviewed. These cases were analyzed in depth. The remaining 286 case interviews subsequently submitted to CDC were reviewed for demographic characteristics and symptom category to assure that their exclusion from the in-depth analysis would be unlikely to bias the findings. The demographic characteristics and symptom categories of the two groups were similar. Although some fairly minor differences were found between the two groups, these differences were not felt to be substantial enough to affect the overall conclusions.

Overall, the 517 interviewed complainants were predominantly white (96%), female (76%), and between the ages of 21 and 60 years (79%). Complainants were approximately 1.5 times more likely to be female and 2.5 times more likely to be women between the ages of 20 and 59 than expected from 1980 census estimates. The overrepresentation of women reporting symptoms could not be explained with available data.

Reports came from all geographic regions of the country, with a heavier than expected concentration of cases from Arizona, where the possibility of aspartame use leading to illness received particularly extensive press coverage. Although aspartame-containing products are widely distributed in the United States and are likely to be consumed by millions of users, there is no specific marketing information available as to who were likely users and/or what groups were most likely to consume the largest per-capita amounts of aspartame. Thus, CDC is unable to estimate a specific complaint rate in relation to the actual number of users.

From the records analyzed in depth, the most commonly reported specific symptoms were headaches, mood alterations, insomnia, dizziness, and fatigue. Overall, 28% of all complainants reported experiencing symptoms on more than one occasion after an intervening symptom-free period. Slightly less than half of these individuals reported that symptoms occurred after using different aspartame-containing products.

In summary, currently available information, based on data with limitations as described in the report, indicates a wide variety of complaints that are generally of a mild nature. Although it may be that certain individuals have an unusual sensitivity to the product, these data do not provide evidence for the existence of serious, widespread, adverse health consequences attendant to the use of aspartame. These principal findings have been summarized in a report published by CDC in the November 2, 1984 issue of the Morbidity and Mortality Weekly Report. With your permission, I will provide a copy for the record.

Mr. Chairman, I will be happy to answer any questions you or other members of the Committee may have.

The CHAIRMAN. Thank you, doctor.

Dr. Wurtman, we will turn to you now. We will take the testimony of all three first and then go to questions.

STATEMENT OF RICHARD J. WURTMAN, M.D., PROFESSOR OF NEUROENDOCRINE REGULATION, MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Dr. WURTMAN. I am a physician and a research scientist, a neuroscientist. I am also the director-to-be of MIT's research hospital.

For the last 15 years, I have been studying the effects of various food constituents on the chemistry of the brain and on various brain functions and behavior. I do these studies on animals, normal people, and people with various diseases. A major goal of this research is to come up with new types of treatments using nutrients as drugs. Actually, Mr. Chairman, I think you and I have had some correspondence about the relation of food constituents like aluminum or lecithin to Alzheimer's disease.

My interest in aspartame derives from the fact that it contains two amino acids, phenylalanine and aspartic acid. Aspartame's consumption raises the levels of these amino acids in the bloodstream, and one of them—phenylalanine—thereupon produces chemical changes in the brain. When you consume aspartame, you don't get the other 20 amino acids that are found in all dietary proteins, and which normally compete with phenylalanine for passage from the blood to the brain. So even a small amount of phenylalanine can have a large effect on brain phenylalanine levels.

The consumption of aspartame might also, by changing brain phenylalanine levels, affect the production of neurotransmitters. These are the chemicals that brain cells use to send signals from one nerve cell to another.

My concern about aspartame has then to do with its possible ability to change brain levels of phenylalanine and other amino acids and thereby to change brain neurotransmitters and brain function.

I became especially concerned when aspartame was introduced into soft drinks because one could predict—and indeed, it has turned out—that its average consumption would go up considerably. I think the amounts actually consumed by some individual people on some hot days are underestimated by using average annual consumption data.

My laboratory started doing pilot studies on these possible effects of aspartame about 2 years ago, and in 1984, we were lucky to get an NIH grant through the Neurology Institute to study this topic systematically. My only support for aspartame research, I hasten to add, comes from the Government, from the National Institutes of Health.

I mention parenthetically that about 10 or 15 percent of my laboratory support does come from industries that have some stake in what you all decide to do. None of that support is for aspartame research. I feel no pressure from them. I wouldn't take the money if I did.

I think that I can summarize my laboratory's findings and their implications in four points: First, in rats, aspartame consumption in doses similar to those that are actually consumed by some people on some days, does indeed affect the production and the release of several brain neurotransmitters—some of these data are published; some of these data are not yet published—and thereby can modify a number of brain functions like the control of blood pressure and several types of behavior.

These effects are enhanced if the aspartame is consumed along with a dietary carbohydrate. Now, that may sound funny. Why would you take aspartame with a carbohydrate? Imagine a child having some diet Kool-Aid with some cookies. I have seen it with my own eyes.

Second, when normal human volunteers consume——

Senator **Metzenbaum**. Would you say again what you said you saw with your own eyes?

Dr. **Wurtman**. I have seen people, not children, but I have seen associates in my laboratory drink diet sodas—thin people—drink diet sodas with doughnuts, or while they have their lunch of sandwiches, peanut butter and jelly sandwiches, et cetera. So it is not absurd to propose that people might consume carbohydrates along with aspartame. People do.

The second point is that when normal human volunteers consume aspartame, changes in brain chemistry are also very likely to occur. We can say this because we have found that reasonable aspartame doses do produce changes in blood amino acid levels which we know are associated with parallel changes in brain amino acids.

The problem is that the human body metabolizes aspartame very differently from the rat's body, and so we really cannot predict from our rat data exactly what the changes will be in the human brain and what the behavioral consequences would be. I think it is important to obtain information about human brain changes after aspartame consumption, but I don't think that the lack of this information is, in itself, a reason for restricting the use of aspartame.

Now, a certain number of consumers or their physicians believe that they have suffered serious neurological or behavioral problems subsequent to consuming large amounts of aspartame, usually a gram or more. As we have heard, it is virtually impossible to assess the significance of these complaints just by examining individual case reports.

The CDC has proposed controlled clinical studies, for instance, on people that think they may have had an aspartame-facilitated seizure. I strongly concur, and I hope that some mechanism can be worked out by which laboratories like my own can get the resources needed to study these people. These mechanisms do not now exist.

Finally, I think the major problem with aspartame use at the present time is the lack of adequate labeling, the fact that one cannot examine those two cans of diet soda there, and tell that one of them, the Diet Coke, contains five times as much aspartame as the other one, the Tab. You can tell that they both have aspartame, but there is nothing on the labels that gives you the dose of aspartame. I think that physicians and consumers have to know the amounts they are consuming, for several reasons.

First, there are a lot of people who are terribly worried about aspartame side-effects who should not be, because they are only taking 10 or 20 milligrams per day. Knowledge of that fact would reassure them.

Second, there will be many people who would like to limit their intake, let's say, to half a gram a day. If the amounts were put on the can, they could tell.

Third, there are physicians who believe that their patients' signs and symptoms may have been caused by aspartame consumption. Such physicians are presently completely unable at present to estimate their amount of aspartame the patient has taken.

I happened to be at an Alzheimer's disease meeting in Israel last week, and while I was there, I picked up a bottle of a diet soft drink. You have copies of its label, I think. I think that that label is a model for what I would like to see done here.

The diet soft drinks in Israel—which, I am told, have had good consumer acceptance—indicate the quantity of aspartame that is present. They suggest a maximum daily dose which I think is rather heroic; 3 grams a day, or about 18 cans of Diet Coke; which would provide a 65-pound child with 100 milligrams per kilogram. For the beverage, which is important because the aspartame breaks down in warm environments to not-fully known products. They suggest an expiration date. I think something like this might be a model for what I would like to see take place here.

Other than idiosyncratic reactions, I think the only concerns that one has to have at this time is for people who take very high dosages on particular days, or people who are also taking various drugs—for psychiatric, neurologic, or cardiovascular illnesses—with which aspartame might interact. I believe that labeling will help us to obviate that problem. It will also help to make physicians cognizant of the fact that some of their patients ought to limit their aspartame intakes.

[The prepared statement of Dr. Wurtman and responses to questions submitted by Senators Dodd and Grassley follow:]

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Richard J. Wurtman, M.D.
Professor of
Neuroendocrine Regulation

Room E25-604
Cambridge, Massachusetts 02139 U.S
Tel. (617) 253-6731
Telex 921473

STATEMENT TO SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES
SENATOR ORRIN G. HATCH, CHAIRMAN

MARCH 19, 1985

Thank you for inviting me to comment on issues raised concerning the safety of aspartame when used as an artificial sweetener.

I am a physician, a research scientist, and a professor of neuroendocrinology and neuropharmacology at the Massachusetts Institute of Technology. For the past 15 years, much of my research has dealt with the effects of food constituents on the chemical composition of the brain, and on various brain functions and types of behavior. I have studied these effects in experimental animals, normal people, and people with brain disorders. My interest in aspartame derives from the fact that it contains two amino acids, phenylalanine and aspartic acid. Aspartame's consumption raises the levels of these amino acids in the blood stream, and one of them - phenylalanine - thereupon produces chemical changes in the brain. In 1980 I was invited to testify before the Board of Inquiry on aspartame, convened by the Food and Drug Administration, concerning the possibility that the aspartic acid in aspartame might do damage to the brain. I concluded then and continue to believe that there is no significant risk of toxicity from the aspartic acid in aspartame. Subsequently, however, I became concerned about risks that might result from the phenylalanine in aspartame, especially if - as seemed likely - the introduction of aspartame into soft drinks would increase the quantities that some people consumed beyond the FDA's consumption estimates (for example, on a hot day). My laboratory initiated pilot studies on this question about two years ago, and in July of 1984 we received a grant from the National Institute of Neurological and Communicative Diseases and Stroke to extend these studies.

I believe that the information now available about aspartame warrants the following conclusions about its possible effects on the brain:

1. When aspartame is consumed by laboratory rats in doses consonant with those sometimes ingested by people, it changes the chemical composition of the brain: It alters the brain's levels of some amino acids, and thereby affects the production and release of some of the neurotransmitters that the brain uses to carry signals from one nerve cell to another. These changes are enhanced when the aspartame is consumed along with a food that is rich in carbohydrate (as happens, for example, when someone eats a jelly sandwich or cookies or pasta along with diet soda). The changes in neurotransmitter release are likely to affect numerous brain functions (like the control of blood pressure, or the appetite) and aspects of behavior.

2.When normal human volunteers consume aspartame in doses that are high - but within the FDA's estimates of 90th percentile intakes - blood amino acid levels change in ways that almost certainly produce corresponding alterations in the chemical composition of their brains (especially if the aspartame has been ingested along with carbohydrate-rich foods). However the particular changes that occur in the human's brain are likely to be different from those occurring in the rat's. (This is because the rat's liver destroys the phenylalanine in aspartame very quickly, while the human's liver destroys the phenylalanine much more slowly. The predominant effect of aspartame on the human's brain is likely to be an increase in its phenylalanine levels; the predominant effect on the rat's brain has been shown to be an increase in its levels of tyrosine, another amino acid that is formed when the liver metabolizes phenylalanine.) Hence, while it seems likely that aspartame, in doses of sufficient size, will affect brain functions and behavior in people, the precise nature of its effects cannot necessarily be predicted using data from experiments on rats. It is necessary also to do functional and behavioral studies on people, - normal people; people with metabolic disorders that impair their ability to metabolize phenylalanine; and people with brain disorders that might sensitize them to whatever changes in brain chemistry the aspartame might produce.

3. Such studies are essential before we can state categorically that aspartame does not affect the brain. However - in the absence of positive evidence that aspartame produces deleterious effects, their performance would not seem to be a prerequisite to the continued general use of aspartame. Of greater concern are the numerous anecdotal reports, written by consumers (and, in some cases, physicians), suggesting a relationship between their consumption of aspartame-sweetened foods and the subsequent appearance of various neurological and behavioral sequellae. A recent report prepared by the Center for Disease Control for the Food and Drug Administration summarized the contents of several hundred such letters; it concluded that the question of whether the sweetener can cause the signs and symptoms that have been ascribed to it can be resolved only by "controlled clinical studies", carried out in medical research centers. (In such studies, patients would alternately receive aspartame and a placebo, double-blind, while their physical condition was being carefully monitored.) I agree with the CDC and the FDA that it is imperative that such studies now be done. I also agree that, even though the evidence for a causal relationship (between aspartame consumption and subsequent behavioral or neurological symptoms, as described by some patients) is, in some cases, highly suggestive, such uncontrolled, anecdotal case reports provide an insufficient basis for limiting aspartame's use.

4. If aspartame does produce side-effects involving the brain, and if these side-effects result from the sweetener's phenylalanine content, then their production almost certainly requires that large amounts of aspartame - probably several grams - be consumed. The problem at present is that it is difficult if not impossible for the patient or his physician to know how much aspartame he has eaten or drunk. A can of diet soda is required to indicate that it contains aspartame, but nowhere on the can need it be stated how much aspartame it contains. I doubt that one consumer (or physician) in a thousand now realizes, for example, that a can of TAB

provides less than one-fourth as much aspartame as a can of DIET-PEPSI or DIET-COKE. The unavailability of this information causes countless people to worry about aspartame who should not (because they consume only tiny amounts of it). Moreover it deprives consumers (or their physicians) of the ability to calculate how much aspartame they have drunk on days when they think the sweetener might have caused side-effects; and it deprives them of the opportunity to set reasonable limits on their aspartame intake. I believe it is essential that companies which include aspartame in their products be required to indicate on the labels (in readable print) how much of the sweetener is present in each can or serving. This simple change in labeling practice would, I believe, sharply reduce the number of consumers who believe without probable foundation that they have suffered aspartame-related side-effects. Perhaps more importantly, it would also enable physicians to identify those patients who might really have had such responses, so that such people might then undergo controlled clinical testing.

Thank you again for giving me this opportunity to express these views.

Richard J. Wurtman, M.D.
Professor, MIT

MASSACHUSETTS INSTITUTE OF TECHNOLOGY

Richard J. Wurtman, M.D.
Professor of
Neuroendocrine Regulation

Room E25-604
Cambridge, Massachusetts 02139 U.S.A.
Tel. (617) 253-6731
Telex 921473

April 13, 1985

Mr. W. Douglas Campbell
Counsel
United States Senate
Committee on Labor and Human
Resources
Washington, D.C., 20510

Dear Mr. Campbell:

Unfortunately your letter of April 4 arrived here only on April 11, at a time when I was out of town. I'm sorry about the delay in responding to Senator Dodd's questions, and will be more than happy to provide additional information, by telephone or in person, ie he wishes.

1. I wouldn't know how to go about establishing a "safe dose" for a carcinogen, - probably in large part because that's not my field of competence. As a non-expert on saccharin, though, I couldn't help wondering, during the hearings, about whether adequate data are available on the carcinogenicity of heated saccharin (a possibly-important question since one of the perceived virtues of this compound, over aspartane, is its ability to withstand heating, so that it can be used, for example, in pastries. Most compounds tend to break down when heated. One wonders whether saccharin might also do so, perhaps generating compounds more carcinogenic than it is.
   I also wondered whether any FDA-mandated studies have been done on the possible carcinogenicity of mixtures of saccharin and phenylalanine or aspartic acid (the amino acids in aspartame) - present, for example, in Tab. One knows that the toxicities of combinations are often very different from those of individual ingredients. Moreover there is some evidence that saccharin's carcinogenicity, when given alone, involves another amino acid, tryptophan.

2. (The Newsweek article wasn't attached.) I am aware of two investigators who have studied the effects of aspartame on the behavior of children. Both are in the Washington area: Dr. Keith Connors, at D.C. Children's Hospital, and Dr. Judith Rapoport, at the NIH, in Bethesda. Some of

Dr. Connors' findings were described in Jane Brody's article on aspartame that appeared a month or so ago in the New York Times.

Thank you again for inviting me to participate in these very important deliberations.

Cordially yours,

Richard J. Wurtman, M.D.

Question for Dr. Wurtman: submitted by Senator Grassley

You noted in your statement that consumption of aspartame by humans almost certainly produces changes in the chemical composition of the brain. In laymen's terms, what does this mean? Is it possible to say what the consequences are in terms of emotional and cognitive functioning?

High-dose aspartame consumption almost certainly changes the ability of certain brain cells to release their neurotransmitters. We can guess as to the consequences by considering what happens when these same neurotransmitters are affected by drugs or diseases. It might be anticipated in normal people that consumption of large amounts of aspartame (for example, on a hot day) might affect sleep, appetite, mood - but probably not to a very significant extent in most people.

Of much greater concern is possible effects in special populations, like: 1) People who are taking certain drugs, for psychiatric, neurologic, or medical illness. The phenylalanine in aspartame might impair the effectiveness of drugs like L-dopa (Parkinson's disease) or Aldomet (hypertension); other drugs (like MAO inhibitors) might cause the aspartame itself to generate potentially-dangerous products in the body.

2) People who - unknown to themselves - have one (of two) abnormal gene for the disease phenylketonuria (PKU). In these people, any dose of aspartame would have twice the usual effect on brain phenylalanine. (Unfortunately, people have no way of knowing whether or not they carry this gene unless they have already given birth to a child with homozygous PKU.

3) People who - unknown to themselves, happen to have a low seizure threshold. While an association between high-dose aspartame consumption and seizure tendency is still quite far from being proved, various well-documented case studies suggest an association, in some people, between high aspartame intake and the occurrence of first-ever seizures (usually in young adults) who have no underlying anatomic basis for the seizures. It can be conjectured that the chemical changes the aspartame produces in the brain deprive the brain of neurotransmitter which normally tend to keep seizure thresholds high. This remains only a conjecture, but I believe the likelihood of the association being real is great enough to warrant causing people with a history or, say, childhood seizures to limit their aspartame intake. Quantity labeling is essential for such voluntary limiting of intake to occur.

The **Chairman**. Thank you, Dr. Wurtman.

Dr. Stegink.

STATEMENT OF LEWIS STEGINK, PH.D., PROFESSOR, DEPARTMENT OF BIOCHEMISTRY AND PEDIATRICS, UNIVERSITY OF IOWA COLLEGE OF MEDICINE

Dr. **Stegink**. My name is Lewis D. Stegink. I am a professor in the departments of biochemistry and pediatrics at the University of Iowa College of Medicine.

Aspartame is the methyl-ester of a dipeptide that combines phenylalanine and aspartic acid, two naturally occurring amino acids found in foods that we eat daily.

When ingested, aspartame is metabolized to its component parts, aspartic acid, phenylalanine, and methanol, all constituents of our normal diet.

Aspartame has been extensively tested in animals and humans and has undergone painstaking regulatory review. In approving aspartame in 1981, the FDA stated that few compounds have withstood such detailed testing and repeated close scrutiny. This opinion was reaffirmed by the FDA when it approved aspartame for use in carbonated beverages in July 1983.

The safety of aspartame has been affirmed by both the FDA and by regulatory authorities around the world. Typically, approval of a food additive is based on safety studies done with laboratory animals. In the case of aspartame, such animal studies were followed by extensive clinical testing in humans.

Over the last 10 years, my colleagues and I at the University of Iowa have conducted extensive clinical studies on aspartame. A brief description of our research follows. A more detailed report was attached to the written statement submitted.

In our studies, aspartame was administered to adults in single doses of 34, 50, 100, 150, and 200 milligrams of aspartame per kilogram of body weight. In other words, a 70-kilogram person, one weighing about 154 pounds, received at the highest dose 14,000 milligrams of aspartame in a single dose. A dose of this magnitude would be the equivalent to eating approximately 5.5 pounds of sugar at a single setting.

In these studies, we measured blood levels of phenylalanine, aspartic acid, and methanol to determine if concentrations reached values known or considered to be toxic. As expected, blood levels of these compounds increased in proportion to the amount of compound given.

However, blood levels did not reach concentrations that would be considered toxic, even at the highest dose. When 34 milligrams of aspartame per kilogram body weight were ingested as a single dose, blood levels were similar to those noted after eating an ordinary meal.

We also studied groups of individuals that were of special interest regarding the safety of aspartame. For example, studies in 1-year-old infants showed that they metabolized aspartame as well as adults. Studies in lactating women demonstrated that the component amino acids of aspartame did not accumulate in milk.

We also carried out studies of individuals heteryzygous for the rare genetic disease called phenylketonuria, or PKU. Individuals with phenylketonuria have virtually no ability to metabolize phenylalanine. Parents of such children have approximately one-half of the normal amount of the enzymatic activity necessary to metabolize phenylalanine, and are called heterozygotes.

Heterozygotes might have difficulty metabolizing increased amounts of dietary phenylalanine. Our studies demonstrated that such individuals adequately metabolize aspartame and that blood phenylalanine levels did not reach values considered to be toxic. On the basis of these data, I have concluded that aspartame is safe at expected levels of consumption.

We selected a dose of 34 milligrams per kilogram body weight as the base line for our studies because it would be the 99th percentile of estimated daily consumption of aspartame across all age groups. This means that 99 out of 100 people will consume this amount or less in a day.

Possible aspartame intake was also calculated assuming that aspartame sweetness would replace total sucrose or sugar sweetness in all foods. This conservative assumption overestimates aspartame use because aspartame cannot substitute for sugar in all food applications. For example, aspartame is not suitable for baking.

Not surprisingly, current market research studies of aspartame consumption indicate values well below this 99th percentile estimate. However, even if an individual on any given day were to exceed the 34-milligram-per-kilogram body weight ingestion level by consuming six times as much as this 99th percentile estimate, our studies in humans ingesting a single dose of 200 milligrams per kilogram body weight indicate no adverse effects.

Since the studies described so far did not evaluate the effects of successive intake of aspartame, we recently elected to study the effects of drinking the equivalent of three to three-and-one-half 12-ounce cans of aspartame-sweetened beverage at 2-hour intervals.

In this study, each subject ingested three successive servings at 2-hour intervals over a period of 6 hours. This was equivalent to a daily consumption of nine to 10 cans of diet soda. These studies demonstrated that blood levels of aspartame metabolites remained within the normal range observed following ingestion of a typical meal.

The report from the Centers for Disease Control, as you have heard, indicates that there is no scientific basis to conclude that there is an obvious relationship between reported illness and aspartame use. Our studies on blood levels of aspartame's metabolites, as well as clinical studies done by others, are consistent with this conclusion and do not provide a basis for suggesting that there are obvious ill effects from aspartame consumption for the general population.

[The prepared statement of Dr. Stegink follows:]

PREPARED STATEMENT OF LEWIS D. STEGINK, PH.D., PROFESSOR OF BIOCHEMISTRY AND PEDIATRICS, THE UNIVERSITY OF IOWA COLLEGE OF MEDICINE, IOWA CITY, IA

My name is Lewis D. Stegink. I am a Professor in the departments of Pediatrics and Biochemistry at the University of Iowa College of Medicine. I received my Ph.D. in Biochemistry from the University of Michigan in 1963 and have been a member of the staff or faculty of the University of Iowa, College of Medicine since that time. Along with my colleague, Dr. L. J. Filer, Jr., I am co-editor of the book "Aspartame" and author of the chapter entitled "Aspartame Metabolism in Humans: Acute Dosing Studies". A copy of that chapter is attached to my statement; it summarizes much of the clinical work done by the University of Iowa research group in our testing of the safety of aspartame in humans. In addition to the book on aspartame, I have co-authored over 100 articles on the metabolism of foods and food additives.

Aspartame is the methyl-ester of a dipeptide that combines L-phenylalanine and L-aspartic acid, two naturally occurring amino acids found in foods that we eat daily. When ingested, aspartame is metabolized to its constituent parts - aspartic acid, phenylalanine and methanol - all components of our normal diet. Aspartame has been extensively tested in animals and humans and has undergone painstaking regulatory review. In approving aspartame in 1981, the FDA stated "Few compounds have withstood such detailed testing and repeated close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety". This opinion was reaffirmed by the FDA when it approved aspartame for use in carbonated beverages in July, 1983.

The safety of aspartame has been affirmed by both the FDA and by regulatory authorities around the world. Most recently, the European Common Market affirmed the safety of aspartame.

Typically, approval of a food additive is based on safety studies done with laboratory animals. In the case of aspartame, such animal studies were followed by extensive clinical testing in humans. Over the last ten years, my colleagues and I at the University of Iowa, as well as other investigators, have conducted extensive clinical studies on aspartame. A brief description of our research follows; a more complete report is attached to this written statement.

In our studies, aspartame was administered to adults in single doses of 34, 50, 100, 150 and 200 mg of aspartame per kilogram of body weight. In other words, a 70 kg person, one weighing 154 pounds, received at the highest dose, 14,000 mgs of aspartame in a single dose. A dose of this magnitude would be equivalent to eating approximately 5.5 pounds of sugar at one time or, in excess of 300 packets of the tabletop sweetener Equal or, 25 quarts of a beverage fully sweetened with aspartame.

In these studies, we measured blood levels of phenylalanine, aspartic acid and methanol to determine if concentrations reached values known or considered to be toxic. As expected, blood levels of these compounds increased in proportion to the amount given. However, blood levels did not reach concentrations that would be considered toxic, even at the highest dose. When 34 mg of aspartame per kilogram body weight were ingested as a single dose, blood levels were similar to those noted after eating an ordinary meal.

We also studied groups of individuals that were of special interest regarding the safety of aspartame. For example, studies in one-year-old infants showed that they metabolized aspartame as well as adults. Studies in lactating women demonstrated that the component amino acids of aspartame did not accumulate in milk. We also carried out studies of individuals heterozygous for the rare genetic disease called phenylketonuria. Individuals with phenylketonuria have virtually no ability to metabolize phenylalanine. Parents of such children have approximately one-half of the normal amount of the enzymatic activity necessary to metabolize phenylalanine, and are called heterozygotes. Heterozygotes might have difficulty metabolizing increased amounts of dietary phenylalanine. Our studies demonstrated that such individuals adequately metabolize aspartame and that blood phenylalanine values did not reach levels considered to be toxic. On the basis of these data, I have concluded that asparatme is safe at expected levels of consumption.

We selected a dose of 34 mg aspartame per kilogram body weight as the baseline for our studies because it would be the 99th percentile of estimated daily consumption of aspartame across all age groups. This means that 99 out of 100 people will consume this amount or less in a day. Possible aspartame intake was calculated assuming that aspartame sweetness would replace total sucrose or sugar sweetness in all foods. This conservative assumption over-estimates aspartame use because aspartame cannot substitute for sugar in all food applications. For example, aspartame is not suitable for baking. Not surprisingly, current market research studies of aspartame consumption indicate values well below this 99th percentile estimate. However, even if an individual on any given day were to exceed the 34 mg/kg body weight ingestion level by consuming six times as much as this 99th percentile estimate, our studies in humans ingesting a single dose of 200 mg/kg body weight indicate no adverse effect.

Since the studies described so far did not evaluate the effects of successive intake of aspartame, we elected to study the effects of drinking the equivalent of three to three and one-half 12 oz. cans of aspartame-sweetened beverage at two hour intervals. In this study, each subject ingested three successive servings at two hour intervals over a period of six hours. This was equivalent to a daily consumption of nine or ten cans of diet soda. These studies demonstrated that blood levels of aspartame metabolites remained within the normal range observed following ingestion a typical meal.

The report from the Center for Disease Control indicates that there is no scientific basis to conclude that there is a relationship between reported illnesses and aspartame use. Our studies on blood levels of aspartame's metabolites, as well as clinical studies done by others, are consistent with this conclusion and do not provide a basis for suggesting that there are obvious ill-effects from aspartame consumption.

A question has been raised as to whether or not aspartame consumption might lead to changes in amino acid and neurotransmitter concentrations in the brain. It has been suggested that ingestion of aspartame under certain circumstances may change blood levels of phenylalanine sufficient to alter brain biochemistry and possibly, human behavior. Such predictions are based on studies in rats investigating the effects of increased plasma phenylalanine levels on the ratio of plasma phenylalanine levels to plasma levels of other large neutral amino acids. While this is an interesting area for further research on the influence of diet on human behavior, this hypothesis, does not alter my conclusion that aspartame is safe. In collaboration with colleagues at the University of Illinoios Medical Center, we fed infant monkeys aspartame at levels up to 3 g per kg body weight for 9 months. In those animals, the ratio of plasma phenylalanine to plasma levels of other large neutral amino acids was affected, but the animals grew and behaved normally. My colleagues and I have also calculated the ratio of phenylalanine to other large neutral amino acids in our studies of normal individuals ingesting repeated servings of aspartame-sweetened beverage. Under these circumstances this ratio remained within the normal range and would not therefore be expected to produce the hypothetical effect on brain biochemistry and behavior.

In conclusion, based on our research, I concur with the findings of the FDA and regulatory authorities around the world that aspartame is safe at expected levels of consumption.

The **Chairman**. Dr. Stegink, your time is up. Thank you very much, and we will put your full statement in the record.

Let me ask the three of you some questions, and then Senator Metzenbaum has some questions. I know this is a very important issue.

Dr. Trowbridge, based on the clinical studies already done and the nature of the complaints and the lack of a pattern for the complaints with regard to aspartame, is there any indication of a significant problem with adverse reactions to aspartame?

Dr. **Trowbridge**. We did not find many case reports of serious adverse reactions. The majority of our complaints were headaches, gastrointestinal upsets, skin rashes, and so forth.

There were some more serious complaints, such as the nine cases of seizures reported, and we included these in our full report as case histories.

The difficulty in evaluating these reports is that one might expect that there would be a certain number, which is difficult to determine, of seizure episodes that would just be occurring in the normal course of events, and that people might associate those seizures with the consumption of aspartame.

It was very difficult, in fact impossible, with the data we had to identify any causal relationship between the aspartame and the seizures as an example.

The **Chairman**. Let me ask Dr. Wurtman a question. Your testimony contains a recommendation that the quantity of aspartame in specific products be included on the product labels. FDA Commissioner Young and Dr. Sanford Miller testified earlier that FDA is willing to consider this recommendation and that it has the authority to require that type of labeling.

Do you have any objections to FDA's consideration of your recommendations if this would be deemed appropriate and necessary?

Dr. **Wurtman**. I would be delighted.

The **Chairman**. You would be happy?

Dr. **Wurtman**. Yes.

Senator **Metzenbaum**. What is your question?

The **Chairman**. Whether his suggestion be considered through the normal administrative processes, since FDA does have the authority to do this.

Dr. **Wurtman**. I don't know what those processes are, but I would be delighted to utilize them if they lead speedily to labeling.

The **Chairman**. As I understand it, the amino acid components of aspartame occur naturally in foods. Therefore, why would not individuals show the same effects from consumption of aspartame as they would from consumption of these same amino acids in other food products?

Dr. **Wurtman**. When you have aspartame, you are not obtaining any of the other amino acids—which are present in all proteins (aspartame is not a protein)—that block phenylalanine's ability to pass from the blood to the brain. So even a small increase in blood phenylalanine will cause a very large increase in brain phenylalanine. To my knowledge, no other food that mankind has ever eaten causes the changes in brain chemistry that are provided by asparatame.

The **Chairman**. In view of the fact that phenylalanine occurs naturally in foods, does it follow that you would recommend that these foods be labeled, also?

Dr. **Wurtman**. No, no. Because, once again, the phenylalanine in foods has virtually no effect on brain phenylalanine levels because those foods also have the other amino acids that keep it from getting into the brain.

The **Chairman**. Dr. Stegink, in the tests that you did in which very high levels of aspartame were administered to adults, did you observe, or did the subjects who were observed report behavioral changes similar to those investigated by the Centers for Disease Control?

Dr. **Stegink**. We did not observe obvious symptoms of that type. The only symptom that we did observe was that subjects who ingested the highest dose complained of a sense of nausea, which is explicable when one understands that this dose of aspartame would be equivalent to ingesting 5.5 pounds of sugar in a single setting. I think the nausea is understandable, and we would be reluctant to conclude that that is a side effect of normal aspartame ingestion levels.

The **Chairman**. Am I correct that the normal diet of children contains, proportional to body weight, much more phenylalanine than that of adults?

Dr. **Stegink**. That is correct. Growth is one of the most important metabolic components of the child's life. Amino acids are required to make the body protein needed for that growth. Thus, it is obvious that the infant not only ingests much but requires much more.

The **Chairman**. Would not the percent of change in the amount of phenylalanine from ingesting aspartame ordinarily be less than the percent change for adults?

Dr. **Stegink**. Not if the dose is given on a milligram-per-kilogram body weight basis which is the way that we would study the compound in comparison studies. In other words, we would compare it at an equivalent dose per kilogram of body weight, which is basically per metabolic mass.

The **Chairman**. Would you react, then, to Dr. Wurtman's comment that the effect of phenylalanine delivered by aspartame is different from the effect of phenylalanine in the normal diet because of the presence in food of other amino acids?

Dr. **Stegink**. What Dr. Wurtman says is correct. When you ingest phenylalanine or a phenylalanine-containing compound alone, the ratio of phenylalanine to the large neutral amino acids as it is called, does increase. On the other hand, if you would ingest the equivalent amount of phenylalanine as part of a protein meal, levels both of phenylalanine and the other amino acids increase, and you would see a different kind of effect.

I would like to point out that the differences between Dr. Wurtman's point of view and mine are relatively minor. I think we both agree that there is no evidence that aspartame is harmful at current levels of ingestion.

The behavior question, I think we both agree, is interesting and should be studied further. I think Dr. Wurtman and I probably differ on the probability of finding such an effect, and that is largely because each of us prefers to use our own data. [Laughter.]

I place greater emphasis on our own monkey and human data where very large doses failed to produce obvious behavioral changes. Searle's rat data indicate that obvious behavioral changes only occur in the presence of very high doses of aspartume.

Behavioral studies carried out by another team at the University of Iowa investigated the effects of aspartame ingestion and hyperactivity in children. These studies were negative. The lack of effect has been confirmed by Judith Rappaport at NIH.

Further, the changes in the brain neurochemistry are unlikely to be noted at the levels likely to be ingested. This even includes the doses administered in our repeated beverage study. I think the question comes down to whether you ingest the aspartame all at once or whether you spread it out over the day. The changes in the ratio are very small when the dose is spread out over the entire day.

On the other hand, Dr. Wurtman places a greater emphasis on his rat data, extrapolating changes in rat brain neurochemistry to possible changes in rat behavior and to possible changes in human behavior.

But I think that basically, overall, we agree on the overall safety of aspartame. We both agree that there are probably only minor risks, in fact, realy no risk at all for the general population. However, we both recognize that there may be a subset of the population which may be susceptible to some adverse effects.

The **Chairman**. Dr. Wurtman, do you agree with that?

Dr. **Wurtman**. As the Committee knows, I am a physician, licensed to practice in the State of Massachusetts; I am also the director-designate of MIT's research hospital, and a clinical associate in medicine at the Massachusetts General Hospital. I have been trained to diagnose and treat neurological and behavioral signs and symptoms in people. My research on aspartame has involved both experimental animals and people. Dr. Stegink is not a physician, but a Ph.D.. His training has not included the recognition and treatment of neurologic problems; indeed, if, after giving aspartame, he thought he noticed anything peculiar about his subjects' behavior, he would be very well advised to obtain the assistance of a physician immediately. I mention this because of the erroneous suggestion that my concerns about aspartame-induced side effects arise solely from my experimental studies on rats. Dr. Stegink has things backward: he's the Ph.D; I'm the M.D.

I disagree with Dr. Stegink about the probable consumption levels. While it's probably true that most people average 8, 10, or 12 milligrams per kilogram per day, I know of people who, for weeks or months, have routinely consumed 5 and even 10 times as much. If people consumed half a gram per day, that wouldn't worry me.

The **Chairman**. How many cans per day?

Dr. **Wurtman**. That is two or three cans per day. But I know better than to believe that everyone restricts their consumption to this amount. I have information from the soft drink industry suggestion that occasional people may have 25 cans of one of those two beverages per day, or a child may drink two liters of diet Kool-Aid, thus obtaining a much higher dose than 8 or 10 milligrams per kilogram.

Now, the problem, I think, has to do with the way the data are collected. If you average the annual consumption divided by the number of people, then you get a fairly low estimate. What concerns me, though, is the possibility that on certain days, let's say a hot day, somebody might be playing tennis and drinking very large amounts of Diet Coke or Tab or whatever, and receive 3 grams or more of aspartame per day.

Again, I think we can obviate that problem by indicating that there is a limit to what people should take, and as long as they stay within that limit, then I guess Dr. Stegink and I are in agreement. I also think that people should discuss their aspartame consumption with their doctor, especially if they are taking medications like MAO inhibitors or L-Dopa or Aldomet.

The **CHAIRMAN**. All right. Senator Metzenbaum.

Senator **METZENBAUM**. Dr. Trowbridge, he always needles me that I ought to be brief, and then I just wanted to point out to him that he wasn't so brief himself. [Laughter.]

The **CHAIRMAN**. He is only interested in brevity at the end of the day. It is the first 4 hours——

Senator **METZENBAUM**. No, no; only brevity when he is asking the questions. [Laughter.]

The **CHAIRMAN**. That is right.

Senator **METZENBAUM**. Does your report on NutraSweet say that NutraSweet is safe?

Dr. **TROWBRIDGE**. We found that there was no basis for identifying any broad public health problem related to the consumption of NutraSweet based on the data we had.

Senator **METZENBAUM**. A little reverse; that is the corollary. That is, did you find that it was unsafe? But I was asking, did you find it was safe?

Dr. **TROWBRIDGE**. The data really are quite limited for a positive statement of that sort, and our conclusion has been that to test individual sensitivities, which we cannot exclude, you would have to do more careful controlled studies.

Senator **METZENBAUM**. And in fact, didn't you say that currently available information based on data with limitations as described do not provide evidence for the existence of serious, widespread adverse health consequences attendant to the use of aspartame, and then you go on to say the only way to be sure is with focused clinical studies? Is that right?

Dr. **TROWBRIDGE**. That is correct.

Senator **METZENBAUM**. And so you feel that more information is needed, more studies are needed, and that they should be done by CDC or FDA?

Dr. **TROWBRIDGE**. We feel that in order to identify whether individuals have particular sensitivities, that further studies would be needed. CDC's role has been to undertake this investigation at FDA's request, and it would be for FDA, who has the regulatory responsibility, to decide whether, for regulatory purposes, further studies were required.

Senator **METZENBAUM**. You think that would be the right thing to do?

Dr. **TROWBRIDGE**. I think it would help to clarify this issue of individual sensitivity.

Senator **METZENBAUM**. Has the FDA made such a request of you at this point?

Dr. **TROWBRIDGE**. No; and I don't believe that our agency would be the proper one in that we have conducted broad population-level epidemiologic studies, but we are not in a position to do the kinds of focused clinical studies that have been proposed.

Senator **METZENBAUM**. Who could do such studies?

Dr. **TROWBRIDGE**. Again, I wouldn't presume to identify that specifically. Certainly the NIH or other investigators that might be funded by the NIH or through FDA might be possible sources of such studies.

Senator **METZENBAUM**. Your report did not in any way examine brain chemistry or cancer issues, but rather investigated consumer complaints of headaches, menstrual problems, heart palpitations, that type of thing. Is that correct?

Dr. **TROWBRIDGE**. It is a broad range of symptoms; that is correct.

Senator **METZENBAUM**. Dr. Wurtman, the chairman asked you whether you would be satisfied on this issue of labeling if there were a follow-up and that the FDA followed its usual procedures in order to provide for labeling of the quantity of aspartame in products, and you indicated your response was in the affirmative.

Was that on the assumption that FDA would then in turn follow through and indeed provide for such labeling after they had gone through whatever procedures they do go through, but that there indeed would be labeling as a result?

Dr. **WURTMAN**. Yes, sir.

Senator **METZENBAUM**. And would you have any difficulty in this committee and the Congress concluding that labeling as to the exact amount of aspartame in a product would be placed on the label, and would you not think that that would expedite the procedure and be a move in the right direction?

Dr. **WURTMAN**. Yes, sir. I think it would be very wrong to consider the matter and then not order quantity labeling, because the implication would be that there is no limit on the amount that people can take.

Senator **METZENBAUM**. I am sorry. I didn't——

Dr. **WURTMAN**. I think that if the question of labeling were brought up and then the decision was made not to label, the implied meaning there was that people should not be concerned with the quantity that they consumed. I think that would be wrong.

Senator **METZENBAUM**. I noticed that in Israel—you presented us with a copy of some labels there—and on the cans there, they say, "Expiring date, 2 months after production," and then they also indicate, "Contains phenylalanine. Do not consume more than 3 grams aspartame daily per adult," and then they indicate to you how much is in each can. In this instance, it is .05 gram.

Do you think that such labeling would be important and valuable in our country?

Dr. **WURTMAN**. Yes, sir; I think the three particular types of information each would be important. First, it should be possible to look at the can and know how many milligrams of aspartame are present in it, in big print.

Second, I think some sort of a commission ought to advise as to what an acceptable upper limit of daily intake would be for the general population. I don't know where that 3-gram figure came from.

Senator METZENBAUM. What would you think is the right figure?

Dr. WURTMAN. Well, I think that up to 1 gram per day, which is 6 cans of Diet Coke, or about 20 cans of Tab, will not elevate plasma amino acid ratios beyond the range that would cause me to worry, so I would be very happy with one gram per day. One gram, I think, would cap the present estimates as to actual use.

Senator METZENBAUM. Do you have an opinion on that subject, Dr. Trowbridge?

Dr. TROWBRIDGE. Our research has not been in the area of the metabolic effects of aspartame consumption, so I wouldn't be able to comment on that.

Senator METZENBAUM. Dr. Stegink, do you have an opinion?

Dr. STEGINK. My own personal opinion is that the FDA's ADI is appropriate as currently set at 50 milligrams per kilogram body weight.

Senator METZENBAUM. Fifty milligrams?

Dr. STEGINK. That number is based upon animal data which basically take the highest no-effect dose seen with a compound, which approximates 5 grams per kilogram body weight, and apply a 100-to-1 correction factor to account for species variation and come to a value which I believe is approximately 50 milligrams per kilogram body weight. I am not sure whether it is officially called an ADI in the United States or not.

Senator METZENBAUM. Dr. Stegink, I am not sure that I understood what you said. What do you think that the maximum daily intake for human beings should be?

Dr. STEGINK. What maximum daily intake do I think is advisable?

Senator METZENBAUM. The limit.

Dr. STEGINK. Well, our data indicate that a dose of 200 milligrams per kilogram body weight as a single dose did not produce obvious adverse effects.

Senator METZENBAUM. That is not what I am asking you, doctor. What do you think is the maximum intake? You are talking about kilograms, and I am asking you what—now, in Israel, they say that——

Dr. STEGINK. Three grams. That means that a 60-kilogram individual would ingest about 50 milligrams per kilogram body weight, so that basically the Israeli numbers are very similar to those that the FDA currently recommends.

Senator METZENBAUM. Which would be 20 milligrams?

Dr. STEGINK. Which would be 50 milligrams per kilogram body weight.

Senator METZENBAUM. I am sorry, I meant to say 50.

Dr. STEGINK. Fifty times 60 is 3,000.

Senator METZENBAUM. Fifty milligrams?

Dr. STEGINK. Correct, per kilogram body weight.

Senator METZENBAUM. But we don't think about that. You know, we don't go around——

Dr. STEGINK. Well, 3,000 milligrams is 3 grams.

Senator **METZENBAUM**. What would you think we ought to put on the can?

Dr. **STEGINK**. Well, Senator, I am in favor of nutritional labeling. However, I would like to see broader based labeling than merely listing the aspartame content.

Senator **METZENBAUM**. I am not opposed to that.

Dr. **STEGINK**. I would like to see sodium, sucrose, saccharin, fiber, fat——

Senator **METZENBAUM**. I will be glad to have you come in and testify for my other bill, but let's stick to this one. [Laughter.]

I have such a bill, but let's just talk about this one. Do you think that the permissible limit ought to be 50 milligrams, or is that 50 milligrams per kilogram of weight?

Dr. **STEGINK**. That is 50 milligrams per kilogram body weight, or for a 60-kilogram individual, which is an average-sized individual, it would be about 3 grams per day.

Senator **METZENBAUM**. Three?

Dr. **STEGINK**. Three, which comes out to the same value as that on the Israeli label which you have in front of you.

Senator **METZENBAUM**. I understand.

Dr. **STEGINK**. In fact that number is probably derived from the same data base used to calculate the U.S. ADI.

Senator **METZENBAUM**. Dr. Wurtman?

Dr. **WURTMAN**. Sir, I think excellent scientists of good will can disagree among themselves as to what the upper limits should be. We are all speculating here. I think if a number of us had a conference for 3 or 4 hours and considered various criteria for assessing maximal doses, we could probably come up with a consensus figure.

This is the first time the question has been raised to me. I would be delighted to serve on a committee charged with advising the FDA about the upper limit for aspartame intake.

Senator **METZENBAUM**. Well, would you all agree that there could be a very positive value to indicating the amount of aspartame, saccharin, cyclamates, or maybe even including sugar, that should be stated on the cans or on food products?

Dr. **STEGINK**. I think that would be useful in terms of the consumer knowing what they are ingesting.

Senator **METZENBAUM**. And you, Dr. Wurtman?

Dr. **WURTMAN**. Yes.

Senator **METZENBAUM**. Dr. Trowbridge, you would agree?

Dr. **TROWBRIDGE**. That would be reasonable.

Senator **METZENBAUM**. That machine doesn't take a nod of the head. [Laughter.]

Dr. **TROWBRIDGE**. Yes.

Senator **METZENBAUM**. All right.

And, Dr. Stegink, am I correct that you are an industry consultant in this field?

Dr. **STEGINK**. I don't know what an industry consultant means. Let me put it this way, Senator. When we heard about the development of aspartame we immediatly raised the question as to whether it was safe for children. Obviously, that is a prime concern for someone who is in a department of pediatrics.

We outlined a series of studies to address questions that we did not feel were answered in the original food additive petition. We proposed animal studies first, and studies in normal volunteers second, and studies in subjects at potential risk, third. Finally, after all of those earlier data were accumulated and evaluated, leading us to feel that there was no risk, were studies carried out in children.

So, yes, indeed, many of our studies were sponsored by G.D. Searle, the manufacturer of the compound. They were paid for by Searle, and I think that is appropriate. However, they were carried out according to our specifications and the results were published in the open refereed literature with my signature on them as a bond.

I would remind you that reproducibility of data is the hallmark of science. Science is like an inverted pyramid. Scientists build upon the stones that others set. Data that are not correct are immediately obvious. A scientist, regardless of his support, is a fool to present data that are not correct.

Senator **METZENBAUM**. Dr. Stegink, I was not impugning your integrity or anything close to it. I was actually building a case for my discussions subsequently with the chairman that we ought to provide something with respect to labeling on cans that contain aspartame, and pointing out to him how credible you are.

Dr. **STEGINK**. Perhaps I am a little sensitive. I have heard that question start and proceed in a different direction.

Senator **METZENBAUM**. All right. We may have some questions to submit. I am very grateful to all of these witnesses for making themselves available, and I would guess that we might have other questions.

[Response of Dr. Trowbridge to question submitted by Senator Grassley follows:]

DR. TROWBRIDGE'S RESPONSE TO THE QUESTION SUBMITTED BY SENATOR GRASSLEY IN REGARD TO A TESTIMONY ON ASPARTAME

Question. Do you recommend further study of the effects of aspartame on humans?

Answer. As indicated in the CDC report to FDA on consumer complaints related to aspartame, the available data cannot exclude the possibility that some individuals have a particular sensitivity to aspartame in comonly consumed amounts. In order to further evaluate this possibility we have recommended in our report that the appropriate studies would be clinical trials in which aspartame was given to individuals reporting such reactions under well-controlled conditions.

The **CHAIRMAN**. Thank you, Senator.

Thank you. We appreciate your coming and appreciate the testimony you have given.

I understand that the next panel is composed of three witnesses who will offer the viewpoints of various users and consumers of artificial sweeteners.

First will be Dr. Ronald Arky, representing the American Diabetes Foundation. Next we will hear from Dr. Michael Jacobson of the Center for Science in the Public Interest. The final witness will be Dr. Howard Roberts, vice president for Science and Technology of the National Soft Drink Association, and formerly Director of the Bureau of Foods at the Food and Drug Administration.

Gentlemen, both Senator Metzenbaum and I were supposed to be finished a long time ago, and I have missed about four appointments this afternoon. We are going to put all of your statements in the record. We would like you to summarize in just a couple of minutes apiece, 2 minutes each, and then, hopefully, we will have very few questions.

So, let's start with you, Dr. Arky. I understand that you have a plane to catch very shortly, so we will start with you and we will ask any questions we have of you first and then let you go.

STATEMENT OF DR. RONALD ARKY, CHIEF OF MEDICINE, MOUNT AUBURN HOSPITAL, ON BEHALF OF THE AMERICAN DIABETES ASSOCIATION

Dr. **Arky**. Thank you.

I am Dr. Arky, and I am representing the American Diabetes Association as the past president and as an individual who has been active in the area of food and nutrition with that association.

Since 1877, when saccharin was introduced, the diabetics as a group have been the major segment of the population who have made use of that substance.

The use of saccharin by diabetics was particularly of concern to us in 1977 when, after the Canadian studies alleged that carcinoma of the bladder, cancer of the bladder, was more evident in a group of animals studied, the American Diabetes Association took its first stand on the topic.

The accumulation of data by a scientific advisory board, and a review of all the literature in the English language available at that time brought the association to conclude that although there was still much work to be done, the data available did not, at least the human data, did not justify a ban, and the association then suggested a moratorium on that ban.

In a subsequent year, we polled the population of diabetics in the United States through the lay journal or magazine, Forecast, and found that over 90 percent of the 11 million diabetics in this country do use, in one form or another, an artificial sweetener, and found that the group actually divides into two segments.

The first, young people who have the insulin-dependent form of diabetes, use sugar substitutes or artificial sweeteners primarily in the setting of social interactions, use soft drinks and so on when they are with their companions and peers.

The second and larger group, individuals who have the type 2 or noninsulin-dependent form of diabetes, who, for the most part in our society, are overweight, utilize artificial sweeteners for purposes of weight loss or to avoid calories.

We have as an association continued to observe carefully the literature, studies, both animal tissue studies, both those in this country and elsewhere, and continue to feel that the data as now available to us would urge that saccharin remain available as has been the case in 1977, 1980, and again today.

Thanks.

[The prepared statement of Dr. Arky follows:]

TESTIMONY
OF
DR. RONALD ALFRED ARKY
FOR THE
AMERICAN DIABETES ASSOCIATION

MR. CHAIRMAN:

Introduction

My name is Ronald A. Arky. I served as President of the American Diabetes Association from 1979 to 1980 and I am a former member of the American Diabetes Association's Board of Directors. I currently serve as a member of the Task Force on Artificial Sweetners appointed by the President of the American Diabetes Association.

I have also served as Chief of the Diabetes and Metabolism Unit at the Thorndike Memorial Laboratory in Boston from 1966 to 1971. Since 1971, I have served as Chief of Medicine at Mt. Auburn Hospital in Cambridge, Massachusetts and I am the Charles S. Davidson Professor of Medicine at Harvard Medical School. I have authored over 95 major articles on the subject of diabetes and metabolism and am a Consulting Editor for the American Journal of Medicine and regularly consult on a number of professional publications in the areas of diabetes and metabolism.

In 1978, The American Diabetes Association was an active participant in the scientific and policy debate regarding saccharin. We have maintained an interest in all artificial sweeteners since they are consumed by large numbers of diabetics. The use of non-nutritive sweeteners has improved the quality of life for individuals with diabetes without question. Yet, we obviously are concerned with possible risks in the use of any foods.

The President of the ADA charged our Committee with reviewing material and issues related to all artificial sweeteners since provisions of the Saccaharin Study and Labeling Act limiting the FDA's ability to restrict the marketing of saccharin expires in April 1985 and since a new artificial sweetener, aspartame, is now used in soft drinks and as a table top sweetener. Our report formed the basis for an update for the ADA position on saccharin and related issues. Our testimony which follows, includes a review of the law, policy and science to date and our position on S.484. I have available for the record a copy of an article published in 1978 reflecting in detail our view of the data at that time.

Legislation 1906-1985

In 1906, the Food and Drug Act contained one provision relating to food safety which stated that a food was deemed adulterated "if it contains any added poisonous or other deleterious ingredient which may render such article injurious to health." In 1938, the Federal Food, Drug, and Cosmetic Act (FDCA) contained similar food safety provisions, and stated that a food shall be deemed to be adulterated:

> "if it contains any poisonous or deleterious substance which may render it injurious to health, but in case the substance is not an added substance, such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to the health."

In 1958, the Food Additives Amendment to the FDCA, which included the "Delaney" anti-cancer clause was passed. This Amendment recognized three basic classes of food additives: (1) those generally recognized as safe (GRAS); (2) those with prior sanction (before 1958); (3) new food and color additives. These are given in Attachment 1 for information.

In April 1977, the Food and Drug Administration (FDA) proposed a ban on saccharin as a food additive because it had been found to cause urinary bladder cancer in experimental animals. There was a loud public outcry, and Congress instituted a moratorium on the proposed ban. In November, 1977, Public Law 95-203, the Saccharin Study and Labelling Act, was enacted. This legislation kept the FDA from prohibiting or restricting the sale or distribution of saccharin for 18 months, based upon the scientific evidence available at the time of the enactment of that law. This provision has been extended for two years on three subsequent occasions, and is due to expire in April, 1985. Specific warnings on labels are required which state: USE OF THIS PRODUCT MAY BE HAZARDOUS TO YOUR HEALTH. THIS PRODUCT CONTAINS SACCHARIN WHICH HAS BEEN DETERMINED TO CAUSE CANCER IN LABORATORY ANIMALS.

ADA Policy Statement: 1978

A Select Committee on Sugar Substitutes, chaired by Ronald K. Kalkhoff, M.D., reviewed the experimental data available through May, 1978, and submitted a report, which was approved by the ADA Scientific Advisory Panel of the Executive Committee, and was published as a Policy Statement in the July-August, 1978 issue of Diabetes Care. The Policy Statement was supplemented by a thorough review of the evidence for and against the carcinogenic potential of saccharin. It was entitled "The Saccharin Controversy," by Drs. R. Kalkhoff and M. Levin, and was published in the same issue of that journal.

The major scientific evidence for the proposed ban were two generation studies in rats, in which the second generation animals, exposed in utero and throughout remaining life, were exposed to saccharin. Bladder carcinoma was included in some animals at saccharin doses of 5% or more in male rats. There were defects in the experimental design, and further studies were recommended, such as dose-response curves and studies of a non-carcinogenic nature.

The Committee concluded that much more research of broader scope and greater detail was needed, and stated: "... based on evidence now available, there appears to be little justification for placing further governmental restrictions on the use of saccharin by the American public at the present time."

Subsequent Developments: 1978-1985

At least three large scale epidemiologic studies in man have shown no association between bladder cancer risk and a history of consumption of artificial sweeteners. Additional studies in animals have shown dose-response relationships and have confirmed that large doses of saccharin (4-5% or above) are associated with a slightly higher incidence of bladder cancer in male rats than in control animals. In utero exposure is not necessary.

Saccharin is the least expensive of the artificial sweeteners, and it can be used in cooking. There is evidence that the percentage of the population now consuming artificial sweeteners is greater than in previous years. It is likely that they are used by a majority of diabetic subjects. It appears that use by young children and females in the child-bearing years is greater than in other individuals, and consumption of artificial sweeteners in soft drinks appears to be increasing in the general population. Some artificial sweeteners cross the placenta. There is no evidence that they cause harm to the fetus; however, some women choose to restrict their use in pregnancy.

In 1980, aspartame was approved for certain purposes. Aspartame was subjected to intense study, and no evidence of carcinogenicity was found. Since aspartame contains phenylalanine, a warning label was required, which states:

"PHENYLKETONURICS: CONTAINS PHENYLALANINE". Concern has been expressed by some scientists that neurochemical changes may occur after aspartame ingestion, and lead to behavioral changes, especially in children. Some scientists have suggested that neurotoxicity may occur. However the FDA found no evidence to support these postulated side effects prior to release of aspartame. Side effects which could be related to aspartame are regularly monitored by the CDC, and to date, no specific side effects from aspartame have been consistently reported. In 1983, aspartame was approved by the FDA as a food additive appropriate for use in soft drinks and in other foods. In soft drinks, it is often mixed with saccharin. Originally, there was concern about methanol toxicity, since the rate of breakdown of aspartame to methanol is increased when carbonated soft drinks are stored in warm climates. However, the amount of methanol is small relative to that found in many everyday foods such as fruit, fruit juices, vegetable soups, beer and wine. Consequently, this is not likely to be a health hazard. There is now a tendency on the part of manufacturers to mix artificial sweeteners to maximize the advantages of each, to control costs, and to decrease total exposure to any one sweetener.

Finally, the status of cyclamates is now under review. Cyclamates were banned in the United States in 1970, on the basis of a 1969 study showing that a mixture of cyclamates and saccharin (10:1) was associated with bladder cancer in rats. Use of cyclamates has continued in Canada. In September, 1982, Abbott Laboratories petitioned the FDA to reassess the status of cyclamates. The Committee on Carcinogenicity of Cyclamates was established by the National Academy of Sciences and the National Research Council at the request of the FDA in order to study the question. The final report is due in March, 1985, and it is possible that cyclamates will be appproved by the FDA and be available for use within a few years.

The net effect of these developments is to provide the consumer with a choice of two major artificial sweeteners (saccharin and aspartame) and with the possibility that a third (cyclamates), may also be available in the near future.

SUMMARY

1. The major benefits of saccharin are an improved quality of life, low cost, and stability at warm temperatures.
2. A small risk for bladder cancer continues to be found in male rats exposed to high doses of saccharin. However, epidemiologic studies show no evidence of a carcinogenic effect in man.

3. Subjects who may be at a higher than normal risk from artificial sweetener ingestion include children and women in the child-bearing years, because ingestion may be greater than in other groups.
4. One alternative sweetener, aspartame, has been approved by the FDA, and a previously banned sweetener, cyclamates, are under reconsideration for approval by the FDA. Their availability will provide the consumer with alternate choices, including the combined use of artificial sweeteners.
5. Extension of the 1977 moratorium PL95-203, still leaves the FDA with legal authority to act against saccharin on the basis of scientific evidence obtained since 1977, in case such evidence should appear.

In view of these considerations, the ADA supports S.484 which extends the limitations on FDA action provided by PL95-203 for another three years. We suggest that all sweeteners be used in a prudent way by childen, by pregnant women, and by women in their child-bearing years because of the greater use by those groups of artificial sweeteners. Combined use of artificial sweeteners should be encouraged. Continued research into possible risks of long term use of saccharin and other sweeteners, either alone or in combination, should continue.

ATTACHMENT 1

The Federal Food, Drug, and Cosmetic Act now contains three anti-cancer clauses. Section 409(c)(3)(A) of the Act, as added by the Food Additives Amendment of 1958 and amended by the Drug Amendments of 1962 states:

> Provided, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal, except that this provision shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production if the Secretary finds (i) that, under the conditions of use and feeding specified in proposed labelling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (ii) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (f) and (g) of this section) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal;

Section 706(b)(5)(B) of the Act, as added by the Color Additives Amendment of 1960 and amended by the Drug Amendments of 1962, states that:

> A color additive (i) shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of safety of additives for use in food, to induce cancer in man or animal, and (ii) shall be deemed unsafe, and shall not be

> listed for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal:
>
> Provided, That clause (i) of this subparagraph (B) shall not apply with respect to the use of a color additive as an ingredient of feed for animals which are raised for food production, if the Secretary finds that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsection (d) of this section) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animal.

Finally, Section 512(d)(1)(H), as added by the Animal Drug Amendments of 1968, states that a new animal application shall not be approved if:

> such drug induces cancer when ingested by man or animal, or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c),(d), and (h) of this section) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals.

These three provisions were enacted by the Congress with the intent of enhancing the safety of the Nation's food supply.

The CHAIRMAN. Thank you so much, doctor.

Let me ask you just one question. Do you feel that the human use of saccharin poses any significant health risk in the humans who use it?

Dr. ARKY. No.

The CHAIRMAN. Senator Metzenbaum?

Senator METZENBAUM. Do you think there would be value in indicating on food products the total amount of saccharin, aspartame, or cyclamates in the product?

Dr. ARKY. Yes.

Senator METZENBAUM. Do you think that the saccharin warning should be more prominently displayed than it has been to date?

Dr. ARKY. I think so, Senator. I must admit to you that, just as so many people, I haven't really gone around and looked, but I think you have pointed out, and, I think, others before you, that it is not very apparent in certain everyday food substances.

Senator METZENBAUM. I thank you, Dr. Arky.

The CHAIRMAN. Thank you, Dr. Arky. You can go catch your plane if you would like. We appreciate having your testimony and your statement.

Dr. Jacobson, we will turn to you next.

STATEMENT OF MICHAEL F. JACOBSON, PH.D., EXECUTIVE DIRECTOR, CENTER FOR SCIENCE IN THE PUBLIC INTEREST

Mr. JACOBSON. Thank you. I will try to be very brief.

There is no disagreement that saccharin causes cancer in animals, and there is some evidence from the National Cancer Institute study that saccharin has also caused bladder cancer in humans. Ideally, saccharin would not be used.

But, as Senator Metzenbaum has pointed out before, if it is banned, aspartame would replace saccharin, and the question is, is the cure worse than the disease? I think the evidence is not in yet as to the relative risks of the two artificial sweeteners.

Of course, one remedy would be to ban both of the sweeteners or treat them the way Canada treated artificial sweeteners for a number of years, allowing it to be purchased at drugstores in packages rather than have it incorporated into foods.

But on the assumption that the moratorium will be extended, I think Congress should take this opportunity to extract some benefits from these hearings and from the opportunities that the situation allows.

I think the Senate and then Congress should put in the bill a requirement for clinical studies of aspartame as well as a better cancer study of aspartame and its metabolites.

Second, the committee should order the Secretary to enforce the current law regarding signs in grocery stores and the legibility of labels. The current law requires signs in at least two and sometimes three places in grocery stores. We surveyed seven stores in the Washington area and found signs at only one of the stores.

Finally, we would suggest two new provisions in the legislation following up on the 1977 Senate Human Resources Committee and the Senate, also: First, warning notices on vending machines. If there are warning notices in grocery stores, they should be on vending machines. The Secretary has the authority to require warnings but has not invoked it. She should be required to do so.

Second, the Senate Human Resources Committee had asked for warning notices in ads, and I would urge that this committee require warning notices in ads for saccharin-containing products.

I think if the Congress does this, it will advance things a little bit. If it is just a pure extension, you will end up here 1 year, 2 years, 3 years later asking the very same questions with the scientists saying the evidence is inconclusive.

[The prepared statement of Mr. Jacobson and response to questions follow:]

Hearing on the Extension of the Saccharin Ban Moratorium
Senate Committee on Labor and Human Resources
April 2, 1985

Michael F. Jacobson, Ph.D.
Executive Director
Center for Science in the Public Interest
1501 16th St. NW
Washington, DC 20036
202-332-9110

Thank you for this opportunity to present our views on the extension of the moratorium on the saccharin ban. CSPI is a non-profit organization that supports improved health and environmental policies. We are supported by over thirty thousand dues-paying members, the sale of educational publications, and foundation grants. I hold a Ph.D. degree in microbiology from M.I.T. and have worked on food safety issues since 1970. Also I have written a book on the use and safety of food additives (Eater's Digest, Doubleday & Co., (1976, 1985)).

There is little disagreement among authoritative agencies that saccharin causes cancer in animals and poses a modest risk of cancer to humans. The Food and Drug Administration, National Institutes of Health, Office of Technology Assessment, and National Academy of Sciences have all concurred on this point.

Where there is disagreement is on the actions that should follow from these scientific findings. The Food, Drug, and Cosmetic Act would ban saccharin, but Congress has temporarily exempted saccharin from the law's requirements.

Inasmuch as there are no proven health benefits from saccharin, we would like to see saccharin out of the food supply. We recognize, however, that some form of extension will be passed, and that replacements for saccharin could prove equally or even more deleterious to consumers. Therefore, we would like to suggest ways in which S.484 could be modified.

The likeliest replacement for most uses of saccharin is aspartame, which is already displacing saccharin at a rapid rate. If aspartame were totally safe and effective, it would be simple to ban many uses of saccharin. However, serious questions have been raised about aspartame's safety. The most pressing questions relate to aspartame's short-term toxic effects. The FDA and citizens groups, including Community Nutrition Institute and my own, have received hundreds of complaints from consumers who say that aspartame-sweetened products caused seizures, headaches, and other problems. The Centers for Disease Control has recommended that clinical experiments be conducted in order to determine the safety of the new sweetener. Such experiments could be conducted within a brief period of time and clarify this major question.

We urge that the current legislation be amended so as to require that the tests that CDC has recommended be conducted promptly and in a thorough manner.

Another change that might occur in the near future is the approval of cyclamate, an artificial sweetener that was banned in 1969, for certain uses. If this occurs, FDA could ban those uses of saccharin.

FDA is also reviewing a petition for yet another artificial sweetener, acesulfame-K, which is already allowed in several European countries. If FDA approves this additive, manufacturers and consumers would have a further choice for low- or non-caloric sweeteners.

Thus, much might happen in the coming months. These prospects justify a much shorter extension than is being proposed in S.484. We suggest that the moratorium be extended for one year, rather than the three years proposed in the bill.

Consumers would benefit significantly from a government study of the comparative risks of saccharin, aspartame, and any other artificial sweeteners that are in use at the time the study is conducted. On the basis of such a study, the government should either ban the most risky sweetener, or if two or more of the sweeteners are considered to have roughly comparable risks, provide consumers with relevant information by means of label notices and literature.

We also recommend that Congress order FDA to enforce the provisions of The Saccharin Study and Labeling Act. The law now stipulates that saccharin-containing foods bear a label warning "in a conspicuous place" and "in conspicuous and legible type in contrast by typography, layout, and color...." The law also requires grocery stores to display "prominently" two or three saccharin warning signs (21 CFR 101.11). Furthermore, the statute gave the Secretary the authority to require similar warning signs on vending machines.

The warning notices on many foods are printed in tiny print and are barely legible. We urge that the Senate report on this bill order the Secretary to survey labels of saccharin-containing foods, require changes in labels that violate the law, and report back to Congress on changes made.

The report should also have the Secretary enforce the regulations requiring signs in grocery stores. We recently surveyed seven grocery stores in the Washington, D.C., area and found only one store in compliance with the law.

The Senate bill, in 1977, had called for warning signs on vending machines, but the House bill did not. The compromise gave the Secretary authority to require signs, but the Secretary has not used that authority. Inasmuch as a high percentage of artificially sweetened soft drinks is sold via vending machines, we urge that the Senate once again pass legislation requiring notices on vending machines. This would result in equal treatment for grocery stores and vending machines and would alert consumers to the presence of saccharin-containing foods.

The Senate Committee on Human Resources recognized in its 1977 report that:

> the effects of a label warning could be overcome by a massive advertising effort on the part of industry. Therefore, in order to fully protect the public's right to informed choice and to provide the maximum information possible, the Committee bill requires all advertisements of saccharin-containing food products to include a health warning message whether the advertising is carried in print or on radio or television.

The committee's foresight deserves recognition. Massive advertising and non-enforcement of the labeling requirements has indeed undermined the desired impact of the law. To correct this situation, we urge that the bill be amended to require an effective warning to be carried in all advertising for saccharin-containing products.

That concludes my formal statement, Chairman Hatch. I would be pleased to answer any questions you might have.

# # #

Questions for Panel Four (Ronald Arky, Michael Jacobson, Howard Roberts) submitted by Senator Grassley

You noted in your statement that children and women in child-bearing years may be at a "higher than normal risk." What is the practical meaning of "higher than normal risk? Would you advocate label warnings addressed to these groups?

Children may be at a higher risk than adults, because they are growing rapidly (their cells are dividing rapidly) and because they would be exposed to saccharin over a longer period of time that someone first consuming saccharin as an adult. Fetuses exposed to saccarin would be in contact with the chemical from the earliest moment possible and are also growing extremely rapidly. Some animal tests have shown that animals exposed to saccharin in utero have a higher cancer risk than those exposed to it after birth.

A label notice offering special advice to pregnant women might be useful.

Michael F. Jacobson, Ph.D.
Executive Director
Center for Science in the
Public Interst
1501-16th Street, NW
Washington, DC 20036
June 17, 1985

Senator METZENBAUM. Dr. Jacobson, how can you possibly have an ad saying, "We're in the Pepsi generation," and then the very next thing say, "Yes, but you'd better recognize that saccharin may be dangerous to your health." It would just totally destroy the whole Pepsi generation, wouldn't it?

Mr. JACOBSON. Well, truth in advertising is sometimes painful, yes, in more ways than just the——

[Laughter.]

Senator METZENBAUM. Would you settle if we put it on the bottle and on the vending machine but——

Mr. JACOBSON. Well, I agree with the Human Resources Committee of 1977, which recommended warnings in advertisements.

The CHAIRMAN. They may take away the commission from Geraldine Ferraro if you keep it up. [Laughter.]

Dr. Roberts.

STATEMENT OF HOWARD R. ROBERTS, PH.D., VICE PRESIDENT, SCIENCE AND TECHNOLOGY, NATIONAL SOFT DRINK ASSOCIATION

Mr. ROBERTS. Unfortunately, I am not from Ohio, but my first name is Howard. [Laughter.]

Senator METZENBAUM. Well, that is a good start.

The CHAIRMAN. You've got it made. [Laughter.]

Mr. ROBERTS. I am very pleased to have this opportunity to testify before this committee, not only on behalf of our industry but also other users of saccharin in the food and beverage, restaurant, pharmaceutical and personal care product industries in support of S. 484.

As we said earlier today, on three separate occasions since 1977, the Congress has voted without any significant dispute or opposition to extend the saccharin moratorium, most recently until April 22, 1985.

The reasons which led the Congress in 1977 to enact the initial moratorium and to extend it ever since then remain valid today. Evidence continues to accumulate to demonstrate that current or anticipated use levels of saccharin do not increase the risk of human cancer. Significant research on saccharin is ongoing. For many purposes, saccharin is the only suitable noncaloric sweetener, and congressional consideration of our food safety laws continues.

We commend the chairman and the ranking minority member for their leadership in sponsoring S. 484, and the other members who have joined in bipartisan support of it. We urge prompt attention to report S. 484 so that it may be enacted by the Senate in a timely fashion.

Again, as was said earlier, saccharin is one of the most thoroughly evaluated of ingredients and is unique among such ingredients with respect to the large body of epidemiological evidence attesting to its safety for human use. It has excellent shelf life; it combines well with other sweeteners and is suitable for use in a variety of applications, including baking and cooking. In many applications, there is simply no available alternative to saccharin.

Today saccharin is used to sweeten a variety of foods and beverages, including those relied upon by diabetics, as we have just heard. It is used in beverages such as fountain diet soft drinks because of its excellent shelf life, in commercial foods which require heat processing, in home cooking and baking, as a table-top sweetener for use in restaurants and in the home. In many instances, saccharin has properties which make it uniquely suitable.

Now, since the approval by FDA of aspartame, some have mistakenly assumed that there is no longer a need for saccharin. This is simply not the case. Neither of the two diet sweeteners is a complete substitute for the other. For example, aspartame cannot be used in cooking or baking, and it gradually loses its sweetness in liquids.

In applications where cooking or baking is required or a long shelf life is desired, saccharin is the low-calorie sweetener of choice. Likewise, aspartame is not, but saccharin is, technologically suited for use in some drug and cosmetic formulations. Aspartame has not, therefore, replaced or eliminated the need for saccharin.

On previous occasions when this committee has considered the saccharin moratorium, the safety record of saccharin has been amply demonstrated, and I think it has been earlier in this hearing as well. I, therefore, will not duplicate the testimony here, but I have submitted additional material in this regard for the record.

I would like to note, however, that research on saccharin designed to elucidate the mechanism of action by which saccharin produces its unique effect, which occurs only after a lifetime of high-dose exposure, and only in the male rat, is ongoing.

The International Life Sciences Institute Saccharin Committee is sponsoring an ambitious program of research in this regard. A review of the safety data on saccharin and a summary of that research program is contained in my testimony which I have submitted for the record.

Passage of S. 484 will provide time to complete this important research so that it may become part of a comprehensive assessment of saccharin at an appropriate future date.

There are two other sweeteners, cyclamate and acesulfame K, as we have heard, which are under review at FDA and may become available commercially for some uses within the next few years. The availability of these sweeteners would permit a multiple-sweetener approach which Commissioner Young talked about in which technological innovation would be facilitated and assurance of safe use enhanced because use would be distributed among several as opposed to a few sweeteners.

In conclusion, then, saccharin has been an important component of the food supply and a valuable ingredient in drug and personal care products for a substantial period of time. It has a long history of safe use, and substantial ongoing research on saccharin holds forth the promise of providing further evidence of safety.

For these three reasons, a continuation of the moratorium is both necessary and justified. Continuation of the moratorium is also desirable so that the Congress can continue considering the complex issue of modernizing Federal food safety laws. This is a most important undertaking for which you, Chairman Hatch, deserve much credit.

Modernization of our food safety laws, which has not been accomplished in over 25 years, is critically needed to permit legal and regulatory policy to reflect the current state of science and technology. Without that modernization, the Congress will find it necessary, as it has in the case of saccharin, to intervene on a case-by-case basis.

I am pleased to have had this opportunity to testify on behalf of the many users of saccharin, and I would be pleased to respond to any questions you may have.

[The prepared statement of Dr. Roberts and a summary statement to accompany his testimony follow:]

STATEMENT
BY
HOWARD R. ROBERTS, PH.D.
VICE PRESIDENT, SCIENCE AND TECHNOLOGY,
NATIONAL SOFT DRINK ASSOCIATION

Mr. Chairman and Members of the Committee:

My name is Howard R. Roberts and I am Vice President, Science and Technology, National Soft Drink Association. I am pleased to have this opportunity to testify before this Committee on behalf of our industry and other users of saccharin in the food and beverage, restaurant, pharmaceutical, and personal care product industries in support of S. 484, a bill to extend the moratorium on banning saccharin for an additional three years.*/

In 1977, after an overwhelming display of public support for saccharin and opposition to the proposal of the Food and Drug Administration to ban it, the Congress enacted the Saccharin Study and Labeling Act, which included a moratorium on any action by FDA to ban saccharin for eighteen months. The initial moratorium was enacted to allow time for further scientific study of saccharin, to ensure the continued availability of various diet or low calorie foods and many important drugs and other consumer products, and to provide time for the Congress to reevaluate food safety policy and consider recommended changes in Federal food safety laws.

On three separate occasions since then, the Congress has voted, without any significant dispute or opposition, to extend the saccharin moratorium. Most recently, the Congress extended the moratorium until April 22, 1985. In so doing, this Committee stated in its Report:

---

*/ A list of industry associations and individual companies that support enactment of S.484 is attached to this testimony.

> This will allow time for completion and review of a solid foundation of research on the safety of saccharin Furthermore, time will be provided for Congress to consider needed revisions to the food safety laws.

The reasons which led the Congress in 1977 to enact the initial moratorium and to extend it ever since then, remain valid today: evidence continues to accumulate to demonstrate that current or anticipated use levels of saccharin do not increase the risk of human cancer;*/ significant research on saccharin is ongoing; for many purposes, saccharin is the only suitable non-caloric sweetener; and, Congressional consideration of our food safety laws continues. The introduction of S. 484 and this opportunity to further demonstrate the continued need for saccharin and the justification for a continued moratorium on efforts to ban it are, therefore, both timely and welcome.

We commend the Chairman and the Ranking Minority Member for their leadership in sponsoring S. 484, and the other Members of this Committee who have joined together in bipartisan support of it. We urge prompt action by this Committee to report S. 484 so that it may be enacted by the Senate in timely fashion.

*/ The availability of aspartame has led to products sweetened with blends of aspartame and saccharin or 100% aspartame, thus significantly reducing the amount of saccharin consumed on an individual basis.

I will now turn to a brief summary of the many reasons why the moratorium should be extended.

The Need for Saccharin Continues

Saccharin is, of course, a non-caloric sweetener which is approximately 300 times sweeter than sugar. It is one of the most thoroughly evaluated of ingredients used in foods and beverages, drugs, and personal care products and is unique among such ingredients with respect to the large body of epidemiological evidence attesting to its safety for human use. It is very versatile, has excellent shelf life, combines well with other sweeteners, and is suitable for use in a variety of applications, including baking and cooking. In many applications, there is simply no other available alternative to saccharin. In others, no alternative exists that is as suitable or attractive.

Today, saccharin is used to sweeten a variety of foods and beverages, including those relied upon by diabetics, persons desirous of controlling their weight and others who need or wish to limit their intake of caloric sweeteners. It is used in beverages such as fountain diet soft drinks because of its excellent shelf life. It is used in commercial foods which require heat processing and in home cooking and baking. It is widely available as a table-top sweetener for use in restaurants and in the home. It is used to make a variety of ingested drugs and cosmetics palatable--

pills, cough syrups, liquid pediatric aspirin, toothpastes, mouthwashes, to name a few examples. In each instance, saccharin has properties which make it uniquely suitable for the particular use. Saccharin's continued availability is therefore essential to the continued availability of a wide array of products which are demanded by, and important to the well-being of, consumers.

Since the approval by FDA of the low-calorie sweetener, aspartame, some persons have mistakenly assumed that there no longer is a need for saccharin. This is simply not the case. Granted, aspartame is an excellent low calorie sweetener; the soft drink industry is using it widely and the consuming public has obviously found its taste and other features to be highly attractive. Nevertheless, neither of the two diet sweeteners is a complete substitute for the other. In point of fact aspartame and saccharin complement one another. For example, aspartame cannot be used in cooking or baking and it breaks down in liquids over time and loses it sweetness. In applications where cooking or baking is required or a long shelf life desired, saccharin is the low calorie sweetener of choice. Likewise, aspartame is not technologically suited for use in some drug and cosmetic formulations, where a low calorie sweetener is essential to the product's taste. The approval and use of aspartame has not, therefore, replaced or eliminated the need for saccharin.

Saccharin is Safe For Use

In the last decade or so, numerous animal and human studies have been conducted to assess the safety of saccharin. Although saccharin has been shown to produce tumors in the bladders of male rats after lifetime exposure to high doses (equivalent to daily consumption of at least 750 cans of diet soft drinks sweetened solely by saccharin), the overwhelming weight of scientific evidence and expert opinion is that saccharin has not been demonstrated to produce any increased risk of cancer in humans and that its continued use at normal consumption levels is indeed safe.

On previous occasions when this Committee has considered saccharin and the moratorium on banning it, the safety record of saccharin has been amply demonstrated. My colleagues have reviewed that record earlier in this hearing as well; I therefore will not duplicate that testimony. I will, however, address briefly the highlights of saccharin's long record of safe use and would be pleased to submit additional material for the record.

Since the 1977 Canadian study which precipitated the FDA effort to ban saccharin, more than a dozen epidemiology (human) studies have been conducted. These studies demonstrate beyond dispute that under the conditions of its use over the past several decades, saccharin has not been shown to increase the risk of human bladder cancer. The epidemiological data base to support that conclusion is one of the largest ever assembled and unquestionably the largest ever for an ingredient of food. This is typified for example by the 1983 study reported in the International Journal of Cancer by Jensen, et. al. which, "provides further evidence that it is highly unlikely that the consumption of artificial sweeteners (saccharin and cyclamate) has contributed to current bladder cancer rates in man."

In addition to the epidemiological work, several animal studies have recently been concluded which further attest to the safety of saccharin at levels well above normal human consumption levels. The large-scale rat study conducted at the IRDC laboratory and reported in 1983*/ was concluded by the investigators to have a no-effect level at a one-percent dose (equivalent to 250 cans of saccharin-sweetened diet soft drink everyday for a lifetime); effects occurred only at dose levels of three percent (750 cans of diet soft drink) and higher. Scientists in the United Kingdom and in the World Health Organization's Joint Expert Committee on Food Additives have concurred in those conclusions. An expert panel of international scientists meeting at Duke University in May, 1983, noted:

> the results of the IRDC study, by better defining the dose-response relationship for bladder tumor

---

*/ A detailed discussion of the IRDC study together with a comprehensive review of the science of saccharin will be published as a special supplement to the April, 1985 issue of Food and Chemical Toxicology.

> risk in the rat, support the conclusion that the present level of exposure of humans to saccharin through its use as a food additive is unlikely to present a cancer risk.

Existing animal evidence points to the thesis that the observed tumors occurred secondary to the physiological stress caused by inappropriately high dosages. These studies further support the proposition that the tumor-inducing effect of saccharin is limited to the male rat bladder.

Ongoing research on saccharin is designed to elucidate this phenomenom by focusing on the mechanism of action by which saccharin produces an effect in the rat. For example, the International Life Sciences Institute-Nutrition Foundation (ILSI-NF) Saccharin Committee is sponsoring an ambitious program of research on saccharin's mechanism of action. This important research is expected to take several years and will provide much additional data on which to assess and understand the unique effect of saccharin in male rats and its relationship to saccharin use in humans. A review of the safety data on saccharin and a summary description of the ILSI-NF saccharin research program is contained in Appendix A to this testimony. Passage of S.484 will provide time to complete this important research so that it may become part of a comprehensive assessment of saccharin at an appropriate future date.

Widespread confidence in the safety of saccharin is further demonstrated by:

- Extensive worldwide use in 96 countries.

- Regulations in the United Kingdom which took effect in September 1983 providing for continued use of saccharin.
- The 1984 approval of the use of saccharin by the Scientific Committee for Food of the Commission of the European Economic Communities after careful evaluation of the entire saccharin data base.
- The 1984 conclusion of the World Health Organization's Joint Expert Committee on Food Additives (JECFA) that the epidemiological studies do not show any evidence that saccharin is a bladder carcinogen.

In short, saccharin is one of the most thoroughly evaluated substances in use today and the extensive body of research data on it are fully supportive of continued safe use by millions of consumers.

Outlook for Other Sweeteners

As I have noted, saccharin's unique properties make its continued availability essential for many diabetics, the weight conscious and other consumers and to the availability of many drugs and personal care products. Saccharin and aspartame complement one another. Two other sweeteners are under review at FDA and may become available commercially for some uses within the next few years. The availability of these sweeteners would permit a "multiple sweetener" approach in which technological innovation would be facilitated and assurance of safe use enhanced because use would be distributed among several, as opposed to a few, sweeteners. The two sweeteners which may be available in a few years are:

- Cyclamate, which came into major use in the 1950's and was used until the precipitious withdrawal of its approval in 1969 is about 30 times sweeter than sugar. Cyclamate is currently under reevaluation by the FDA. After a National Academy of Sciences panel concludes a review of certain scientific issues, it is expected that FDA will begin the process to reapprove it. Given the nature of that process, however, it is unlikely that cyclamate will be available for several years.

- Acesulfame K is a relatively new synthetic sweetener which, like saccharin, is not metabolized and therefore is not caloric; it has intense sweetness, on the order of 200 times that of sugar; it is quite stable, and therefore potentially useful for a variety of applications. FDA is currently reviewing a petition for limited uses -- such as in table top and chewing gum -- approval for expanded uses has not yet been sought.

There are numerous other potential diet sweeteners which are in various stages of development or review.

In no case, however, has the extensive safety testing that would be required for approval been done and petitions filed with the FDA. The prospect, therefore, for an adequate substitute for the many uses of saccharin is not likely in the near future.

Conclusion

Saccharin has been an important component of the food supply, and a valuable ingredient in drug and personal care products for a substantial period of time, and it remains so to this day. It has a history of safe use which is amply supported by both animal and human scientific studies. In addition, substantial ongoing research on saccharin holds forth the promise of a better understanding of the mechanism of action which leads to an increased incidence of tumors in male rat bladders at very high doses. For these three reasons, a continuation of the moratorium is both necessary and justified.

Continuation of the moratorium is desirable from another perspective as well. For several years now, the Congress has been considering the complex issue of modernizing the federal food safety laws. This is an important undertaking by the Congress for which the Chairman deserves much credit. Modernization of our food safety laws is needed to permit legal and regulatory policy to reflect the current state of science and technology. Without that modernization, the Congress will find it necessary, as it has in the case of saccharin, to intervene on a case-by-case basis. We urge this Committee to continue its efforts to make modest, but meaningful revision to our food safety laws. Modernization of those laws would obviate the need for the Congress to deal with saccharin on a case-by-case basis. Until then, extensions of the existing moratorium will be a periodic necessity.

I am pleased to have had this opportunity to testify on behalf of the many users of saccharin and would be pleased to respond to any questions at this time.

* * *

INDUSTRY ASSOCIATIONS AND COMPANIES SUPPORTING ENACTMENT OF S. 484

Industry Associations

National Soft Drink Association

Juvenile Diabetes Foundation

American Diabetes Association

Grocery Manufacturers of America

Cosmetic, Toiletry & Fragrance Association

The Proprietary Association

National Food Processors Association

Individual Companies

The Coca-Cola Company

PepsiCo, Inc.

The Seven-Up Company

Dr Pepper Company

Royal Crown Cola Company

The Procter & Gamble Co.

A&W Beverages, Inc.

Cadbury Schweppes, Inc.

Del Monte Corporation

Sherwin-Williams Chemicals

Cumberland Packing Corp.

APPENDIX A

INTERNATIONAL LIFE SCIENCES INSTITUTE-NUTRITION FOUNDATION
SACCHARIN TECHNICAL COMMITTEE

SACCHARIN RESEARCH PROGRAM

ILSI International Life Sciences Institute-Nutrition Foundation
THE NORTH AMERICAN BRANCH OF THE INTERNATIONAL LIFE SCIENCES INSTITUTE

SACCHARIN RESEARCH PROGRAM

INTRODUCTION

Saccharin has been used by man for nearly one hundred years; however, because of experimental findings in rats, in 1972 the Food and Drug Administration removed saccharin from the list of substances Generally Recognized as Safe (GRAS). Since that time it has been extensively investigated, especially for its effects on the rat bladder and in human use.

It is well established that bladder tumors occur in male Sprague Dawley rats fed saccharin in the diet. However, tumors have been observed only at high dietary doses; they have not been demonstrated in other species and a significant increase in tumor incidence has not been observed in female rats. It is also clear that in rats fed the high levels of saccharin associated with bladder tumors, disturbances in the physiology of the gastrointestinal and urinary tracts are present. Furthermore, the bladder tumors in the rat fed saccharin cannot be explained at the cellular and molecular level on the basis of currently accepted mechanisms of carcinogenicity, since saccharin is non-genotoxic and is not metabolized. It is the view of the

1126 SIXTEENTH STREET, N.W. • SUITE 111 • WASHINGTON, D.C. 20036 • (202) 659-0074/872-0778

Saccharin Technical Committee of the International Life Sciences Institute-Nutrition Foundation (ILSI-NF), therefore, that saccharin is not a classical genotoxic carcinogen, and that tumors occur in the rat only as a consequence of abnormal physiological conditions that are dose-dependent and not relevant to man.

Evidence for the inherent safety of saccharin as currently used has been provided by extensive epidemiological studies in man based on decades of saccharin use. The epidemiological findings have been reviewed recently. The Office of Science and Technology draft White Paper on cancer concluded, "saccharin use was not a significant public health problem" (OST, 1982). Similarly the Duke Expert Panel on Saccharin (1983) interpreted the epidemiological finding as "providing evidence that saccharin has not increased the risk of bladder cancer in man." Morgan (1983) states that "most epidemiologists are confident that artificial sweeteners do not represent a public health hazard for bladder cancers."

The objectives of the ILSI-NF saccharin research program are to extend the data base on saccharin safety and to determine, if possible, the mechanisms that underlie the bladder tumors which occur when extreme doses of saccharin are fed in the diet to the male rat. The following is an outline of the areas of research considered most important to these objectives, an indication of the studies under consideration and a summary of the scientific basis with respect to saccharin safety.

REVIEW OF CARCINOGENICITY AND OTHER STUDIES ON SACCHARIN

Species

During the past decade long-term studies of saccharin have been conducted in the mouse, rat, hamster and monkey. These studies have been summarized in the IARC Monograph (1980) and Cranmer (1980). It had been held, as a result of earlier studies, that administration of saccharin over two generations was essential for bladder tumor formation in the rat. In only one of these earlier studies (Arnold et al., 1980) was there a significantly increased tumor incidence in the F_0 generation. The IRDC study (1983) has shown no significant difference in tumor incidence in the rat with either one or two-generation saccharin treatment regimens. None of the long-term studies in species other than the rat have been positive for bladder cancers. These latter studies have been criticized on grounds such as too low dosages, too few animals, inadequate reporting, etc. (Munro, 1983). Long-term studies of saccharin have recently been completed in the mouse by NCTR and in the hamster by FDA. These studies may provide additional information with regard to species specificity. If bladder tumors occur when saccharin is fed to species other than the rat, it is surprising that such tumors were not seen in at least one of the published studies in the mouse or hamster.

Dosage Levels

A high dosage of saccharin is critical to the development of bladder tumors in the male rat. Of the studies in which positive findings have been observed, the tumor incidence was significantly increased at 5% (Arnold et al., 1980); 5% (Tisdel et al., 1974); 7.5% (Taylor and Friedman, 1974). The IRDC study (1983) tested saccharin in the male rat at dosage levels of 1.00, 3.00, 4.00, 5.00, 6.25 and 7.50% in the diet. The tumor response in this study decreased rapidly with reductions in dose level. In the initial review of the pathology, a statistically significant incidence of bladder tumors was noted at dose levels of 3.% and above. At the 3.% dose level, significance was obtained when malignant and benign tumors were combined. In a subsequent review of the pathology by Dr. Robert Squire a significant incidence of bladder tumors was found only at dose levels of 4.% and above. Bladder tumors occur in the male rat only when high doses of saccharin have been fed; the physiological alterations associated with these high doses are considered to be mediators of this process.

Dosage Regimen

All of the long-term studies in which positive results have been found have involved a dosage regimen with saccharin incorporated into the animal feed. Chowaniec and Hicks (1979) did not observe tumors in the bladders of male Wistar rats fed 2 g/kg body weight saccharin in the drinking water. In the same study they found an increase in the number of tumors in male rats fed 4 g/kg body weight saccharin in the diet although the increase was not statistically significant. Kadlubar et al. (1983) found that female rats fed 2% saccharin in the drinking water consumed four times more saccharin than female rats fed 5% saccharin in the feed, yet this high intake of saccharin did not increase tumor incidence either when fed alone or when fed to MNU-initiated animals. Both sex differences and dosage regimens are factors in these studies, nevertheless they again point to physiological changes as playing an intermediary role as discussed later in this document.

Sex

The relative sensitivity of the male rat to bladder tumors when fed saccharin, compared to the female rat, has been a striking and consistent finding. This is particularly surprising since female rats consume more diet per unit weight than males and thus would be exposed to larger doses of saccharin on a weight basis. Both male and female rats were used in each of the three two-generation carcinogenicity studies of saccharin in which there were positive findings (Arnold et al., 1980; Tisdel et al., 1974; Taylor and Friedman, 1974) but a significantly increased tumor incidence was found only in males. Clearly this difference cannot be related to exposure level. Possible explanations may lie in hormonal differences between the sexes or in sex differences in physiological responses.

Strain Differences

Strain differences are known to be modifying factors in carcinogenesis (Nagasaki et al., 1975; Sontag, 1980) and may be an important factor in the response to high doses of saccharin. Increased incidences of bladder tumors have been reported in four studies of saccharin with Sprague Dawley rats (Arnold et al., 1980; Tisdel et al., 1974; Taylor and Friedman, 1974; and IRDC, 1983). Chowaniec and Hicks (1979) observed a non-significant increase in bladder tumors in male Wistar rats fed saccharin. Fukushima et al. (1983), on the other hand, did not observe bladder tumors in male Sprague Dawley, Wistar or F344 rats fed saccharin in the diet for 52 weeks, while tumors were observed in male ACI rats fed saccharin for this period. Since more than half the ACI rats in the latter study were infected with the bladder parasite *T. crassicauda*, it is difficult to draw conclusions from this study. The lack of consistent effects, even in the male rat, is not currently well understood, but demonstrates the apparent isolated nature of saccharin's effects.

Initiation and Duration of Saccharin Treatment

An analysis of the data from the various long-term rat studies of saccharin suggests that early and continuous exposure to high doses of saccharin is necessary for tumor development. In the two-generation studies that have yielded positive results (Arnold et al., 1980; Tisdel et al., 1974; Taylor and Friedman, 1974; and IRDC, 1983) the F_0 generations were given saccharin in the diet prior to mating, through gestation and lactation and the F_1 generation animals were weaned onto the same diets fed the parents. A separate group of animals in the IRDC study was derived from dams fed graded doses up to 5% saccharin during lactation and the pups weaned onto a diet containing saccharin. There was no significant difference between the tumor incidence in this group and the corresponding group from dams fed the same dose of saccharin in utero and throughout life.

In contrast to these findings, single generation lifetime studies in the rat in which saccharin treatment was initiated after weaning have generally not yielded positive findings (JECFA, 1982). The two-generation feeding protocol or the protocol used by IRDC in which pups were derived from females fed saccharin during lactation and weaned onto a diet containing saccharin, in contrast to a protocol in which saccharin feeding is started at six or eight weeks, may represent an important difference in exposure patterns.

Exposure *in utero* has been shown not to be relevant to the development of bladder tumors in male rats fed saccharin. In contrast, the lactation period appears to be important since significant effects on pup body weight gain have been noted at this time. During this period pups from females fed saccharin would be exposed to saccharin in the milk and via consumption of dry diet (Sweatman and Renwick, 1982). In the period immediately after weaning, rats fed a fixed concentration of saccharin in the diet ingest a level of saccharin that, on a relative weight basis, greatly exceeds the level ingested by mature animals on the same diet. Thus, the immature rat is exposed to massive doses of saccharin during the period of life when they are generally considered most vulnerable to toxic insults. Although lifetime exposure of the rat to saccharin appears to be necessary for expression of bladder tumors, exposure to extreme doses during this early period may be a factor in the pathogenesis of these changes.

Metabolism of Saccharin

Extensive studies by Sweatman and Renwick (1980, 1982), Renwick (1983) and others have made a major contribution to our understanding of the fate of saccharin in animals and man. The overall picture offers few clues as to the mode of action of saccharin but allows us to eliminate several possibilities from our speculation. Saccharin is not metabolized and there is experimental evidence that it does not bind to DNA (Lutz and Schlatter, 1979). In the rat, saccharin is slowly and incompletely absorbed from the intestine and is rapidly eliminated into the urine by glomerular filtration and renal tubular excretion. It has been shown that in the mature rat, after saccharin ingestion, tissue levels are somewhat higher in the kidney and bladder than in plasma while the concentrations in other tissues are lower than those in plasma (Sweatman and Renwick, 1980). Kidney levels of saccharin were markedly higher than plasma at dietary levels greater than 5% due to saturation of renal tubular excretion. The concentrations of saccharin in bladder epithelium and wall were similar in male and female rats at the 5% dietary level. In a similar study conducted in immature rats fed 5% saccharin in the diet, high levels of saccharin were found in the kidney and bladder during the immediate post-weaning period (Sweatman and Renwick, 1982). The high concentrations of saccharin that were found in the urine of these animals may have complicated the tissue analysis; nevertheless, the data do suggest that tissue levels may be high during the period that immature animals would ingest inordinate amounts of saccharin when it is present at a fixed concentration in the diet.

In lifetime studies of saccharin, rats in the immediate post-weaning period are subject to dose levels on a relative basis that greatly exceed those at any other time during life. Urinary concentrations at this time would also be at peak levels.

Studies related to this time period may help to clarify the underlying mechanisms for expression of bladder tumors.

Physiological Changes

Although it is metabolically inert, the ingestion of high levels of saccharin by the rat is associated with a wide spectrum of deviations from physiological normality. In long-term feeding studies in the male rat, dietary saccharin caused an increase in water intake and urine volume and a decrease in urine osmolality. These changes did not occur when saccharin was fed in the drinking water; in this situation water intake and urine volume were reduced and osmolality was increased (West and Jackson, 1981).

Dietary saccharin feeding causes a variety of disturbances in gastrointestinal function of the rat (Anderson and Kirkland, 1980). These include cecal enlargement, increased stool water content, a shift in the ratio of anaerobic to aerobic flora, and marked increases in the concentration of tryptophan and its metabolites in the caecum (Sims and Renwick, 1983). These derangements in gastrointestinal function in the rat occur over the same range of dose levels that result in tumors in long-term studies.

In addition to the gastrointestinal changes, male rats fed high doses of saccharin exhibit a variety of physiological changes in the urinary tract. Male rats that ingested high levels of saccharin in the diet had increased urine volume, decreased osmolality and reduced urinary pH (Schoenig, 1983). These changes were associated with alterations in urine composition and particularly increases in excretion of Ca, Mg and P (Anderson, 1979). Renwick and Sims (1983) found strong evidence for bladder distension in the rat fed a 7.5% dietary level of saccharin. These disturbances in urinary excretion patterns occurred in conjunction with changes in the urothelial mineral balance. Anderson (1983) has shown significantly elevated levels of Na, K, Mg and Zn per unit of dry weight, compared to controls, in the bladder tissue of male rats fed 5.0 and 7.5% saccharin in the diet. These same doses of saccharin did not alter the tissue concentrations of these minerals in female rats. This author also found that excess mineral levels were concentrated primarily in the bladder epithelium compared to muscle, suggesting urine as the probable origin.

Renwick (1983) has found that the abnormal tryptophan metabolism in the gut of rats fed high dietary levels of saccharin is associated with changes in excretory patterns of tryptophan metabolites. Under these conditions indican and indolelactic acid levels were increased in the plasma and indican levels were increased in the milk of lactating female rats and in the urine of F_1 pups. The increased urinary indican excretion of rats fed saccharin beginning as soon as they consumed dry diet was maximal at five weeks, again indicating the extreme doses of saccharin which young animals receive.

The physiological changes summarized above indicate the extensive derangements present in male rats fed saccharin. Sex differences in mineral concentrations in the epithelial cells of the bladder of rats fed saccharin may be important in explaining the sex differences in the incidence of bladder tumors. Differences in the physiological changes that occur have also been observed when saccharin has been fed in the drinking water as opposed to the diet. These observations suggest the possibility of determining, in a suitable rat study, whether it is the exposure to saccharin, per se, that is critical in the development of bladder tumors or whether, as indicated by current data, these tumors are secondary to the aberrant physiology present.

Although the physiological changes which occur in the intestine and urinary tract of male rats fed high dietary levels of saccharin are thought to be associated with bladder tumors in this species, there is no evidence that they are relevant for man. In a recent study, Roberts and Renwick (personal communication) found that a dose of 1 g saccharin per day given for a month to human volunteers caused no changes in urine volume or indican excretion.

Urothelial Changes

The results of studies on the effect of saccharin feeding on the histology of the bladder epithelium are contradictory. Fukushima and Cohen (1980) and Murasaki and Cohen (1981) found that the feeding of 5% saccharin in the diet to F344 rats was followed by vacuolar degeneration of the urothelial cells in three weeks and simple hyperplasia at five weeks. These authors found that the thymidine labeling index was elevated after one week of saccharin feeding and that this increased labeling index was maintained for 18 weeks. They interpreted these findings as indicating damage to the bladder epithelium by saccharin followed by exfoliation of superficial cells and hyperplasia. In contrast to these findings, Reitz et al. (1983) was unable to demonstrate an increased thymidine labeling index in Sprague Dawley rats fed saccharin. It is important, if possible, to resolve these discordant findings with respect to saccharin. Hyperplasia of the bladder epithelium was not a general characteristic of rats fed saccharin in a long-term study (IRDC, 1983).

It is of particular interest that hyperplasia was found in the bladders of male Sprague Dawley rats fed 5% saccharin in the diet but not in rats fed 4% saccharin in the drinking water even though the net intakes of saccharin in both groups was determined to be virtually the same (West and Jackson, 1981). Although the number of animals tested was small, these findings further reinforce the hypothesis that the dosage regimen, and thus differences in physiological changes, may be critical factors in the development of bladder tumors in male rats fed high dosage levels of saccharin.

Cellular Effects

A number of studies have been conducted to elucidate the effects of saccharin at the cellular level. These studies have focused on bladder epithelial membranes, intracellular enzymes and DNA. Although these investigations have demonstrated certain properties of saccharin, they have not suggested a mechanism that would explain the bladder tumors in animals treated with this substance.

Extensive investigations of the genotoxicity of saccharin in short-term tests have been reviewed by Arthur D. Little (1980, 1982) and by Ashby (1983). With minor exceptions, saccharin is consistently negative in the Ames test, either with or without activation or under host-mediated conditions. The results of *in vitro* mammalian cell tests for mutation also appear to be negative. The few positive test results reported have occurred only at very high doses with low cell survival and marginal elevation in mutation frequency.

The results of *in* *vitro* and *in* *vivo* tests of saccharin for chromosome damage have not been consistent. Chromosome aberrations were observed in 13 of 16 in vitro tests using mammalian cells with high concentrations of saccharin. On the other hand, the results of nine in vivo tests at doses of saccharin approximately 2 g/kg have been negative. None of these tests have employed bladder cells; tests using an appropriate bladder cell system might clarify this picture. At present it is not clear whether the chromosome damage observed in vitro represents gene toxicity or some other non-specific effects, e.g., on ion transport or osmolality.

Saccharin is nucleophilic and thus is unlikely to be attracted to or reactive with DNA. Lutz and Schlatter (1977, 1979) showed that saccharin did not bind covalently with DNA of either rat liver or bladder. Miyata et al. ([illegible]0) found that saccharin did not alter the sedimentation profiles of DNA as measured by alkaline sucrose density gradient analysis with or without pretreatment of the cells with BCPN. Kadlubar et al. (1983), furthermore, demonstrated that saccharin did not alter the repair or persistence of alkylated DNA adducts in rat epithelial cells after intravesicular administration of MNU. In contrast to these negative findings, Lindberg and Pinnas (1980) noted a significant concentration-dependent inhibition in repair of UV-damaged DNA in human lymphocytes exposed to saccharin. More recently Milo et al. (1983) found that saccharin, together with N-methylnitrosourea or N-ethylnitrosourea, transformed cultured human foreskin fibroblasts. These results were cell cycle dependent and dependent on the sequence of cellular exposure. These effects are dependent on exposure during a particular phase (S) of the cell cycle. These tests results are difficult to interpret particularly since only limited testing has been conducted with these techniques, and correlations between activity and structure or physical/chemical properties of chemicals are unknown.

Other studies on the mechanism of saccharin's effects have been reported. Lok et al. (1982) found that saccharin was an inhibitor of urease and several proteases *in vitro* and suggested that saccharin may behave like leupeptin, a protease inhibitor that increases the size of chemically-induced bladder cancers. Imaida et al. (1983) found that saccharin increased the membrane potential of rat bladder epithelium at a 5% feeding level. Mosser and Bols (1983) found that, unlike many tumor promotors, saccharin did not affect cell-to-cell metabolic cooperation in cultured human fibroblasts.

CONCLUSIONS

The above review summarizes the saccharin findings critical to the objective and working hypothesis on which the ILSI-NF research program is based. The published information on saccharin effects is often conflicting and difficult to interpret; nevertheless, the weight of the evidence supports certain conclusions that are the basis for our primary research objectives.

1. Extensive epidemiological studies on saccharin have demonstrated that this substance does not represent a public health hazard for man. After reviewing this literature, the Scientific Review Panel at the Duke Conference on Saccharin concluded that "we do not believe that there is a pressing need for new epidemiological studies of the saccharin-bladder cancer association at this time." No further work in this area is contemplated.

2. Saccharin, when fed at high dietary levels to the male rat, is associated with the development of bladder tumors. Bladder tumors have not been observed in mice, hamsters, guinea pigs or monkeys fed saccharin.

3. The feeding of saccharin, at the high doses associated with the develoment of bladder tumors in the rat,

results in physiological disturbances in the gastrointestinal and urinary tracts. Physiological changes in water balance and altered protein and mineral metabolism result in an abnormal milieu in the bladder, the only site of tumor formation in the rat. The decreased osmolality and increased volume of the urine of rats fed high levels of saccharin in the diet is correlated with the ultimate tumor development.

4. The evidence available to date suggests that although lifetime feeding of saccharin to the rat is probably necessary for bladder tumor formation, exposure to saccharin at high dose levels in the early post-natal period may be a factor in the development of bladder tumors. It is during this period, in a lifetime study, that maximum exposure to saccharin would occur and physiological changes would be most severe.

5. A similar statistical increase in bladder tumor incidence has not been observed in female rats fed saccharin at levels that result in tumors in males. The tumorigenic process thus appears to be both sex sensitive and species specific.

6. Although studies are limited, the feeding of saccharin to the female rat in the drinking water at a level of 2% did not result in bladder tumors. The physiological

responses of the rat to high concentrations of saccharin in the drinking water differ markedly from those observed when saccharin is fed in the diet. This points to a correlative study of saccharin dosage regimens and physiological responses as a promising avenue for further research.

7. Saccharin is not electrophilic, is not mutagenic, nor does it bind with DNA. Metabolic studies have also shown that saccharin is not degraded to metabolites that might have such properties.

8. The weight of current evidence suggests that saccharin is associated with bladder tumors in the rat through some as yet undefined secondary mechanism. Among the possibilities considered are changes in bladder cell surface permeability, enzyme function or hormonal function.

9. Since saccharin is associated with bladder tumors only in the male rat and only under conditions of altered physiology, there is considerable doubt that the rat is a relevant model for man. There is a strong possibility that the secondary mechanisms believed to be involved in the rat are related to the inordinately high feeding levels. It is expected that a threshold dose exists below which the secondary mechanisms do not operate.

RESEARCH PROGRAM

The working hypothesis of the ILSI-NF saccharin research program is based on observations that the bladder tumors associated with the feeding of saccharin are sex sensitive, species and organ specific, and appear only at high doses that cause profound alterations to the milieu of the intestinal tract, the kidney, and the bladder cells. This situation suggests that the effects of saccharin are likely to be secondary to physiological and metabolic changes at the level of the intestine, kidney, and bladder epithelium rather than through an intrinsic carcinogenic mechanism.

The research studies on saccharin that have been thus far initiated are briefly described in the following.

ILSI-NF Saccharin Research Status

The research program that is currently being supported by ILSI-NF includes studies in Dr. Andrew Renwick's laboratory at The University of Southampton and studies at Intox Laboratories, Little Rock, Arkansas. Dr. Renwick's research on saccharin is in part a continuation of his earlier program and includes work in the following areas:

a. The effects of saccharin on the functional integrity of the urinary bladder;

b. The effects of saccharin on the microbial catabolism of protein and amino acids;

c. The effects of saccharin on ascorbic acid and glutathione in relation to the bladder.

New studies to be undertaken by Dr. Renwick's group are directed to the effect of saccharin on the metabolism of anutrients with special reference to the neonatal male rat.

The studies that are being initiated at Intox Laboratories are in two areas. A study is being conducted on different salt forms of saccharin to obtain information on the disposition of these materials in the male rat, the physiological changes produced by the salt forms in the urine, and changes in the bladder as indicated by light microscopy, scanning electron microscopy and thymidine labeling index. The main objective of this study is to confirm the observations made by Hasegawa and Cohen (see attached Prepublication copy) on saccharin salt forms and, in addition, to provide information on the influence of sex, diet type, and rat strain in the response to sodium saccharin. In this study, a comparison of differences between the Purina rodent diet and the Agway diet used by Dr. Cohen will be made. In addition, the Sprague Dawley rat will be compared with the F344 rat. Sodium saccharin as well as potassium, calcium and acid saccharin will be evaluated.

A secondary preliminary study on salt forms of saccharin is being conducted to determine the palatability of the sodium, potassium and calcium salts when fed to male and female rats in the drinking water, with and without ammonium chloride. This study is being done to provide information that may be used in further studies on saccharin by the drinking water route.

The second area under investigation at Intox Laboratories is directed to the effects of pre- and postnatal sodium saccharin administration on the metabolic/nutritional status of the neonatal rat. A number of physiological parameters will be evaluated, including growth rate; food and water consumption; urine volume, osmolality and saccharin concentration; cecal weight; fecal moisture; hematology; plasma lipid levels and distribution; plasma Vitamin C levels; hepatic Vitamin A, Vitamin E and folate levels; and bladder morphology, lipid and protein levels. This study should provide information on responses of the neonatal rat with respect to these parameters and data on intra- and interlitter variability for the observed changes.

In addition to the studies outlined above, further mechanistic research on saccharin is under consideration. This research includes studies on sodium saccharin and other salt forms to determine the mechanisms underlying the differences in response to these materials observed in the rat by Hasegawa and Cohen, and to extend these observations to other parameters that may be indicative of tumor responses. Studies on the effect of saccharin salt forms on urine pH, bladder permeability, and urothelial mineral concentrations are also under consideration.

The initial thrust of the ILSI-NF research program will be to clarify, in the rat, the interrelationships between saccharin dosage regimens, chemical form, etc., and the physiological changes that occur in order to affirm those that may mediate the formation of bladder tumors. Extended studies in the rat will be considered if the findings from the short-term studies require confirmation. Consideration may also be given to a long-term study in a species other than the rat; however, recent studies by NCTR in the mouse and by FDA in the hamster may serve to resolve the question of species specificity. The potential value of a further study will be determined when the results of the NCTR and FDA studies are available.

REFERENCES

Anderson, R.L. and Kirkland, J.J., 1980. The effect of sodium saccharin in the diet on caecal microflora. Food Cosmet. Toxicol., 18:353-355.

Anderson, R.L., 1979. Response of male rats to sodium saccharin ingestion: urine composition and mineral balance. Food Cosmet. Toxicol., 17:195-200.

Anderson, R.L., 1983. Some physiological and metabolic effects of ingested sodium saccharin. Proc. European Toxicology Forum, October 18-22, Geneva.

Arnold, D.L., Moodie, C.A., Grice, H.C., Charbonneau, S.M., Stavric, B., Collins, B.T., McGuire, P.F. and Munro, I.C., 1980. Long-term study of orthotoluene sulfonamide and saccharin in the rat. Toxic. Appl. Pharmacol., 52:113-152.

Arthur D. Little, Inc., 1980. Evaluation of short-term mutagenesis and neoplastic transformation studies on saccharin. Unpublished.

Arthur D. Little, Inc., 1982. Evaluation of short-term mutagenesis and neoplastic transformation studies on saccharin. An update. Unpublished.

Ashby, J., 1983. Genotoxicity of saccharin: relevance to bladder cancer. Report of Scientific Review Panel, Duke University Medical Center. Saccharin: An Update.

Carlborg, F.W., 1983. Statistical considerations of the IRDC experiment with saccharin. Proc. European Toxicology Forum, October 18-22, Geneva.

Chowaniec, J. and Hicks, R.M., 1979. Response of the rat to saccharin with particular reference to the urinary bladder. Brit. J. Cancer, 39:55.

Cranmer, M.F., 1980. Saccharin: A Report. Pathotox Publishers, Inc.

Fukushima, S. and Cohen, S.M., 1980. Saccharin-induced hyperplasia of the rat urinary bladder. Cancer Res., 40:734-736.

Fukushima, S., Arai, M., Nakanowatari, J., Hibino, T., Okuda, M. and Ito, N., 1983. Differences in susceptibility to sodium saccharin among various strains of rats and other animal species. GANN, 74:8.

IARC Monograph, 1980. Evaluation of the carcinogenic risk of chemicals to humans. Some non-nutritive sweetening agents. IARC, Lyons.

Imaida, K., Oshima, M., Fukushima, S., Ito, N. and Hotta, K., 1983. Membrane potentials of urinary bladder epithelium in F344 rats treated with N-butyl-N-(4-hydroxybutyl) nitrosamine or sodium saccharin. Carcinogenesis, 4:659-661.

IRDC, 1983. Evaluation of the dose response and *in utero* exposure of saccharin in the rat. Unpublished.

JECFA, 1982. Toxicological evaluation of certain food additives. Twenty-sixth Report of the Joint FAO/WHO Expert Committee on Food Additives, Geneva.

Kadlubar, F., 1983. Unpublished.

Lindberg, R.D. and Pinnas, J.L., 1980. Inhibition of DNA repair by tobacco smoke and saccharin. Fed. Proc., 39:1022.

Lok, E., Iverson, F. and Clayson, D.V., 1982. The inhibition of urease and proteases by sodium saccharin. Cancer Lett., 16:163-169.

Lutz, W.K. and Schlatter, C.H., 1977. Saccharin does not bind to DNA of liver or bladder in the rat. Chem.-Biol. Interact., 19:253-257.

Lutz, W.K. and Schlatter, C.H., 1979. *In vivo* covalent binding of chemicals to DNA as a short term test for carcinogenicity. Arch. Toxicol. Suppl. 2, 411-415.

Milo, G.E., et al., 1983. Co-carcinogenicity of saccharin and N-methylnitrosourea of human diploid fibroblasts. Proc. Am. Assoc. Cancer Res., Abstract no. 404.

Miyata, Y. et al., 1980. Effects of caffeine and saccharin on DNA in the bladder epithelium of rats treated with N-butyl-N-(3-carboxypropyl)-nitrosamine. Chem.-Biol. Interact., 29:291-302.

Morgan, R., 1983. Proceedings of the Toxicology Forum, Geneva, Switzerland, p. 356.

Mosser, D.D. and Bols, N.C., 1983. Effect of saccharin on metabolic cooperation between human fibroblasts. Carcinogenesis, 4:991-995.

Munro, I.C., 1983. Proceedings of the European Toxicology Forum, October 18-22, Geneva.

Murasaki, G. and Cohen, S.M., 1981. Effect of dose of sodium saccharin on the induction of rat urinary bladder proliferation. Cancer Res., 41:942-944.

Nagasaki, H., Kawabata, H., Miyata, Y., Inoue, K., Hirao, K., Aoe, H. and Ito, N., 1975. Effect of various factors on induction of liver tumors in animals by the alpha isomer of benzene hexachloride. GANN, 66:185.

OST, 1982. Regulatory Work Group on Science and Technology, Office of Science and Technology Policy Discussion. Draft - Potential Human Carcinogenesis: Methods for Identification and Characterization, Chapter 3, p. 10, October 1.

Reitz, R.H., Fox, T.R., Quast, J.F., Emerson, J., Lewkowski, J. and Stanley, J., 1983. Food consumption patterns and effects of saccharin upon urinary bladder tissue in very young rats. Unpublished.

Renwick, A.G. and Sims, J., 1983. Distension of the urinary bladder in rats fed saccharin containing diet. Cancer Lett., 18:63-68.

Renwick, A.G., 1983. The fate of saccharin in rat and man. Proc. European Toxicology Forum, October 18-22, Geneva.

Schoenig, G.P., 1983. IRDC study quality assurance and in-life results. To be published.

Scientific Review Panel, Duke University Medical Center, "Saccharin: An Update," May 1983.

Sims, J. and Renwick, A.G., 1983. The effects of saccharin on the metabolism of dietary tryptophan to indole, a known co-carcinogen for the urinary bladder of the rat. Toxicol. Appl. Pharmacol., 67:132-151.

Sontag, J.M., 1980. Experimental identification of genitourinary carcinogens. Urol. Clin. North Am. 7:803.

Sweatman, T.W. and Renwick, A.G., 1980. The tissue distribution and pharmacokinetics of saccharin in the rat. Toxicol. Appl. Pharmacol., 55:18-31.

Sweatman, T.W. and Renwick, A.G., 1982. Tissue levels of saccharin in the rat during two-generation feeding studies. Toxicol. Appl. Pharmacol., 62:465-473.

Taylor, J.M. and Friedman, L., 1974. Combined chronic feeding of three-generation reproduction study of sodium saccharin in the rat. (Abstract no. 200), Toxicol. Appl. Pharmacol., 29:154.

Tisdel, M.O., Nees, P.O., Harris, D.L. and Derse, P.H., 1974. Long-term feeding of saccharin in rats. In: Symposium: Sweeteners, (G.E. Inglett, Ed.), pp. 145-158, C.N. Avi Publishing Company, Westport.

West, R.W. and Jackson, C.D., 1981. Saccharin effects of the urinary physiology and urothelium of the rat when administered in diet or drinking water. Toxicol. Lett., 7:409-416.

THE EFFECT OF DIFFERENT SALTS OF SACCHARIN ON THE RAT URINARY BLADDER

Ryohei Hasegawa and Samuel M. Cohen

Department of Pathology & Laboratory Medicine and The Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, NE 68105.

PREPUBLICATION COPY

For your information only;
not for distribution or other use.

ABSTRACT

Weanling male F344 rats were fed the sodium, potassium, or calcium salt of saccharin or acid saccharin as 5% of the diet by weight for 10 weeks. Sodium saccharin induced urinary bladder epithelial proliferation as determined by the labelling index following ^{3}H-thymidine incorporation (0.55 ± 0.20% compared to 0.06 ± 0.04% in the control group) and by light and scanning electron microscopy. Potassium saccharin also increased the labelling index (0.18 ± 0.09%), but calcium saccharin (0.12 ± 0.11%) and acid saccharin (0.07 ± 0.04%) did not significantly increase the labelling index. These differences in labelling index were not due to differences in saccharin excretion in the urine.

Saccharin, a widely used noncaloric sweetening agent, has been reported to be carcinogenic toward the urinary bladder in male Sprague-Dawley rats when administered as the sodium salt at high doses in the diet over two generations (1). In F344 rats, the feeding of 5% sodium saccharin in the diet resulted in epithelial hyperplasia of the bladder and increased labelling index (2). Saccharin is not mutagenic (3), does not react with DNA (4), and is now recognized as a promoting agent in several two-stage models of bladder carcinogenesis (5,6). The proliferative, promoting, and carcinogenic effects of saccharin are dose related (6-8). In the *in vivo* experiments described above, saccharin was administered to rats in the form of the sodium salt (sodium saccharin). Acid saccharin has been less extensively studied, but has not been found to be carcinogenic in experiments using mice, rats or hamsters (9). Little biological data for the other salts of saccharin are available.

Of the physiological changes caused by sodium saccharin feeding, alterations in tryptophan metabolism (10) and mineral levels in the urine (11) have been discussed with relation to the effects of saccharin. Recently, Fukushima et al. (12) reported that sodium *o*-phenylphenate, but not *o*-phenylphenol, showed significant promoting activity in the bladder of F344 rats pretreated with N-butyl-N-(4-hydroxybutyl)nitrosamine, and they suggested an important role for the sodium salt of chemicals, such as saccharin, *o*-phenylphenol, and ascorbic acid, in urinary bladder carcinogenesis (12,13). The present study was undertaken to determine the proliferative effects of various salts of saccharin administered in the diet, and revealed that the response of the rat urinary bladder differed between them but the amount of saccharin excreted in the urine was not related to the biologic effect.

Male F344 rats (Charles River Inc., Wilmington, MA), 5 weeks old at the start of the experiment, were maintained on diet containing either sodium, potassium, calcium, or acid saccharin at a dose of 5% by weight (14). Food and water were available ad libitum. After 10 weeks, six animals were killed 1 hr after an i.p. injection of ^{3}H-thymidine (1 μCi/g body weight) and the urinary bladder was examined by autoradiography (15). Bladders of another six rats were processed for the observation by light and scanning electron microscopy by method described previously (7,16). The rats given saccharin compounds showed slightly less body weight gain than the control group, and their feces were increased in water content. Calcium and acid saccharin treated rats especially had severe diarrhea during the first few weeks of the experiment.

Proliferative lesions of the urinary bladder are summarized in Table 1. Histologically, simple hyperplasia was observed in several animals administered sodium, potassium, or calcium saccharin. The incidence was significantly higher in rats fed sodium saccharin. More advanced lesions were not induced in any groups, and no remarkable changes were seen in rats fed acid saccharin. The appearance of microvilli, especially pleomorphic microvilli, on the luminal surface of the bladder as observed by scanning electron microscopy is correlated with rapidly proliferating epithelial lesions (16,17). In the present study, pleomorphic microvilli were observed only in rats given sodium saccharin. Uniform microvilli were observed in the bladder of 2 of 6 rats in each of the groups fed potassium or calcium saccharin, but acid saccharin did not result in any surface changes. By autoradiography using [methyl-^{3}H]thymidine, the labelling index (%) in the bladder epithelium was highest following sodium saccharin treatment (0.55 ± 0.20), and slightly increased following potassium saccharin (0.18 ± 0.09) compared to the control group (0.06 ± 0.04). The labelling index for sodium saccharin was significantly greater than that following potassium saccharin. Calcium and acid saccharin failed to significantly increase the labelling index. The saccharin intake was similar in all groups.

In a separate experiment using the same regimen as above, rats were maintained on the saccharin containing diets for 7 and 28 days, and urine and feces were examined for saccharin content as shown in Table 2 using the high performance liquid chromatography (HPLC) method (18). It is well known that saccharin is not metabolized and is excreted rapidly into the urine and feces but not into the air (19, 20). Of the total saccharin excreted in the urine and feces, more than 60% appeared in the urine after sodium and potassium saccharin administration, and less than 50% after calcium and acid saccharin. Interestingly, however, the urinary concentration of saccharin was almost the same in rats given the different forms at each time examined (0.18-0.21 mmole/ml at day 7 and 0.14-0.19 mmole/ml at day 28). These results indicate that the presence in the urine of saccharin is not sufficient for the induction of urinary bladder proliferation as observed in rats fed sodium saccharin. Other changes in the urine resulting from saccharin administration, such as pH or cation concentrations, which vary depending on the form that saccharin is administered, might effect the bioavailability of the saccharin molecule to the bladder epithelium.

Saccharin appears to be absorbed from the urine into the urinary bladder tissue through the epithelium (21). When pregnant rats were administered a single dose of ^{14}C-saccharin on the 21st day of gestation, the ^{14}C cleared more slowly from the urinary bladder than from other maternal and fetal tissues (20). The delay in saccharin elimination from the target organ appears to be a more significant finding with respect to its carcinogenic activity than simply measuring accumulation (22). We examined the concentration of certain cations (sodium, potassium, and calcium ions) in the urine and blood, and pH, creatinine and osmolality of the urine in rats given 5% sodium, potassium, calcium, or acid saccharin in the diet. The proliferative alterations of the bladder epithelium were directly correlated to changes in urinary pH and urinary concentration of sodium ion, and an inverse relationship was seen between urinary calcium concentration and labelling index. Urinary pH was slightly increased following sodium saccharin feeding and decreased with calcium and acid saccharin compared to the control group. Potassium saccharin did not change the pH. Similar correlations between histopathological findings and urinary pH were reported using sodium-o-phenylphenate and o-phenylphenol (12). Sodium ion in the urine was markedly increased by sodium saccharin feeding. Further research will be required to determine whether or not sodium, calcium, hydrogen, or other ions in the urine directly affect the response of the bladder epithelium to the saccharin molecule.

REFERENCES & NOTES

1. D.L. Arnold, C.A. Moodie, H.C. Grice, S.M. Charbonneau, B. Stavric, B.T. Collins, P.F. McGuire, Z.Z. Zawidzka, I.C. Munro, *Toxicol. Appl. Pharmacol.* 52, 113 (1980); M.O. Tisdel, P.O. Nees, D.L. Harris, P.H. Derse, in *Symposium: Sweeteners*, G.E. Inglett, Ed. (C.N. Avi Publishing Co., Westport, 1974), p. 145.
2. S. Fukushima, S.M. Cohen, *Cancer Res.* 40, 734 (1980); S.M. Cohen, G. Murasaki, S. Fukushima, R.E. Greenfield, *Cancer Res.* 42, 65 (1982).
3. J. Ashby, in *Saccharin: An Update* (Report of Scientific Review Panel, Duke Univ. Med. Ctr., 1983).
4. W.K. Lutz, C.H. Schlatter, *Chem.-Biol. Interact.* 19, 253 (1977).
5. R.M. Hicks, J. Chowaniec, *Cancer Res.* 37, 2943 (1977); S.M. Cohen, *Environ. Hlth. Perspec.* 50, 51 (1983).
6. N. Ito, S. Fukushima, T. Shirai, K. Nakanishi, R. Hasegawa, K. Imaida, *Environ. Hlth. Perspec.* 49, 217 (1983).
7. G. Murasaki, S.M. Cohen, *Cancer Res.* 41, 942 (1981).
8. G.P. Schoenig, E.I. Goldenthal, R.G. Geil, C.H. Frith, W.R. Richter, F.W. Carlborg, *Fd. Chem. Toxicol.*, submitted for publication.
9. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Non-Nutritive Sweetening Agents, Vol. 22 (1980).
10. J. Sims, A.G. Renwick, *Toxicol. Appl. Pharmacol.* 67, 132 (1983).
11. R.L. Anderson, *Fd. Cosmet. Toxicol.* 17, 195 (1979); D.M. Demers, S. Fukushima, S.M. Cohen, *Cancer Res.* 41, 103 (1981).
12. S. Fukushima, Y. Kurata, M. Shibata, E. Ikawa, N. Ito, *Gann* 74, 625 (1983).
13. S. Fukushima, A. Hagiwara, T. Ogiso, M. Shibata, N. Ito, *Fd. Chem. Toxicol.* 21, 59 (1983); S. Fukushima, K. Imaida, T. Sakata, T. Okamura, M. Shibata, N. Ito, *Cancer Res.* 43, 4454 (1983).

14. Chemicals were obtained from the following sources and mixed with powdered rat chow (Prolab 3500, Agway Inc., St. Mary's, OH) at a dose of 5% by weight and pelletized (Dyets, Inc., Philadelphia, PA). Sodium saccharin from Sigma Chemical Co., St. Louis, MO; acid saccharin from Aldrich Chemical Co., Milwaukee, WI and potassium and calcium saccharin were kindly provided by Dr. T. Lawson of the Eppley Institute for Research in Cancer and Allied Diseases, Omaha, NE, which were originally obtained from Sherwin Williams Co., Cincinnati, OH.

15. Each rat received a single intraperitoneal injection of [methyl-^{3}H]thymidine (specific activity 20 Ci/mM, New England Nuclear Co., MA) at a dose of 1 μCi/g body weight 1 hr before sacrifice. The bladder was inflated with 10% phosphate buffered formalin and cut into longitudinal strips. Glass slides were dipped in Kodak NTB-2 photographic emulsion, stored in light-proof boxes at 4°C for 2 weeks, and then developed with Kodak D19. The tissues were stained with hematoxylin and eosin. Five thousand bladder epithelial cells were counted in each bladder.

16. S. Fukushima, S.M. Cohen, M. Arai, J.B. Jacobs, G.H. Friedell, *Am. J. Pathol.* 102, 373 (1981).

17. J.B. Jacobs, S.M. Cohen, G.H. Friedell, in *The Pathology of Bladder Cancer*, Vol. 2, G.T. Bryan, S.M. Cohen, Eds. (CRC Press, Boca Raton, FL, 1983), pp. 141-181.

18. Extraction of saccharin was performed according to the method of H.S.I. Tan and P.W.C. Pan (23). Urine (0.5ml) or feces (1 g in dry weight) was mixed with 15 ml of 7.5% HCl in a 50-ml centrifuge tube. Saccharin was extracted into 9 ml of ether by vortexing the tube on a mixer for 5 min. After centrifugation at 220 g for 3 min, the clear supernate was transferred into a 25-ml volmetric flask. The extraction was repeated 2 more times with 8 ml ether and the extract combined in the flask was diluted to volume with

ether, if necessary. A 2.5 ml of this solution was dryed, and the residue was dissolved in 10 ml of water-saturated chloroform and applied on the celite column. This step was repeated 2 more times and the eluate was discarded. The absorbed saccharin was eluted with 50 ml of acetic acid-ethyl acetate-chloroform (1:7.5:25) eluent and the eluate was dried on a rotary evaporator. The residue was dissolved in 5 ml of methanol-water (1:1). Ten µl of the sample solution was chromatographed under the condition of 0.2 a.u.f.s., UV 254 nm, and 1.2 ml/min of flow rate of acetic acid-methanol-water (2.5:100:500) using Waters Associates Model M-6000A liquid chromatograph and Whatman Partisil 10-ODS-2-L HPLC column. As an extract standard, 25 mg of sodium saccharin in water was extracted as described above. Five or 10 µg of sodium saccharin in water was applied on HPLC as a standard solution. Celite column was prepared by placing 2 g of celite (545 AW, Johns-Manville, CO) and then 3 g of celite mixed with 1.5 ml of 0.1M NaOH in a glass chromatographic tube with stopcock.

19. T.W. Sweatman, A.G. Renwick, *Science* 205, 1019 (1979).
20. L.M. Ball, A.G. Renwick, R.T. Williams, *Xenobiotica* 7, 189 (1977).
21. A.G. Renwick, T.W. Sweatman, *J. Pharm. Pharmacol.* 31, 650 (1979).
22. T.W. Sweatman, A.G. Renwick, *Toxicol. Appl. Pharmacol.* 62, 465 (1982).
23. H.S.I. Tan, P.W.C Pan, *J. Chromat.* 238, 500 (1982).
24. We thank Drs. Phillip Issenberg and Terence Lawson for their technical advice and assistance with the HPLC methodology, Dr. Robert E. Greenfield for his advice and comments, Margaret St.John for technical assistance, and Jan Leemkuil for assistance in the preparation of this manuscript. This work was supported in part by USPHS Grants CA32313 and CA32513 from the National Cancer Institute, the latter through the National Bladder Cancer Project.

TABLE 1.

Chemical	Final Body Weight (g)§	Estimated Chemical Intake (g/rat)	Light Microscopy		Scanning Electron Microscopy			Autoradiography	
						Microvilli			
			N	Simple Hyperplasia	N	Uniform	Pleomorphic	N	Labelling Index (%)§
Na - S	271 ± 27	61	12	5*	6	2	2	5	0.55±0.20**
K - S	276 ± 17	65	12	2	6	2	0	6	0.18±0.09†
Ca - S	266 ± 17	59	12	2	6	1	0	6	0.12±0.11
Acid - S	262 ± 14	65	12	0	6	0	0	6	0.07±0.04
Control	281 ± 11	--	12	0	6	0	0	6	0.06±0.04

§ mean ± S.D.

* Significantly different from Acid-S and control groups at $p<0.02$ by Fisher test

** Significantly different from the other groups at $p<0.01$ by Student's t test

† Significancly different from control groups at $p<0.05$ by Student's t test

LEGEND FOR TABLE 1. Proliferative findings in the rat urinary bladder epithelium. Five weeks old male F344 rats (83.7 ± 8.1 g) were given 5% of sodium (Na-S), potassium (K-S), calcium (Ca-S), or acid (Acid-S) saccharin in the diet for 10 weeks (14). Urinary bladders from 6 rats of each group were inflated *in situ* with 2% glutaraldehyde in 0.1 M cacodylate buffer (pH 7.4), and divided in half longitudinally. One half was processed for light microscopy and the other half was processed for scanning electron microscopy. Urinary bladders from the other 6 rats of each group were inflated *in situ* with 10% phosphate buffered formalin 1 hr after intraperitoneal injection of 1 μCi/g body weight of [methyl-^{3}H]-thymidine and processed for autoradiographic examination (15). The epithelial proliferation was apparent in the bladders of rats fed sodium saccharin, significantly less in rats fed potassium saccharin, and was not increased compared to controls in rats fed calcium or acid saccharin.

TABLE 2.

Chemical	Number of Rats	Intake in 24 Hours			URINE			FECES		
						Saccharin§			Saccharin§	
		Diet (g)	Water (ml)	Saccharin (m mole)	Volume (ml)	Concentration (m mole/ml)	Daily Excretion (m mole)	Dry Weight (g)	Concentration (m mole/g)	Daily Excretion (m mole)
At Day 7										
Na-S	6	16.0	26.0	3.55	8.4	0.18±0.04	1.47±0.44	4.3	0.19±0.07	0.78±0.27
K-S	6	16.4	27.7	3.65	8.2	0.19±0.05	1.52±0.28	4.5	0.20±0.10	0.93±0.53
Ca-S	6	16.2	23.2	3.90	4.3	0.20±0.02	0.88±0.15#	5.1	0.24±0.11	1.27±0.66
Acid-S	6	14.8	22.6	4.03	4.4	0.21±0.04	0.96±0.43●	4.7	0.26±0.07	1.23±0.54
Control	6	14.6	16.9	0	4.7	0	0	3.7	0	0
At Day 28										
Na-S	6	19.2	31.6	4.26	10.4	0.17±0.04	1.72±0.43	5.5	0.24±0.05	1.34±0.31
K-S	6	20.6	31.3	4.58	13.5	0.14±0.04	1.72±0.22	5.5	0.22±0.03	1.19±0.16
Ca-S	6	21.3	34.3	5.13	6.3	0.14±0.03	0.87±0.15##	6.8	0.26±0.05	1.75±0.31†
Acid-S	6	22.2	30.5	6.05	8.8	0.19±0.02*	1.70±0.32	6.3	0.29±0.02**	1.86±0.39††
Control	6	17.1	18.2	0	6.7	0	0	4.4	0	0

§ mean ± S.D.

Significantly different from Na-S and K-S groups at $p<0.05$ and $p<0.01$, respectively, by Student's t test

● Significantly different from K-S group at $p<0.05$ by Student's t test

Significantly different from Na-S, K-S, and Acid-S groups at $p<0.01$, $p<0.001$, and $p<0.001$, respectively, by Student's t test

† Significantly different from K-S group at $p<0.01$ by Student's t test

* Significantly different from K-S and Ca-S groups at $p<0.05$ by Student's t test

** Significantly different from K-S group at $p<0.01$ by Student's t test

†† Significantly different from Na-S and K-S groups at $p<0.05$ and $p<0.01$, respectively, by Student's t test

LEGEND FOR TABLE 2. Saccharin excretion into the urine and feces in rats given various forms of saccharin in the diet. After 7 and 28 days of exposure to the saccharin containing diet as described in Table 1, urine samples were collected for 4 hours in the morning without the diet using the metal metabolic cages. The rats were then kept in the same cages for the next 24 hrs with food and water available to collect feces samples and to determine urine and feces volumes and diet and water consumptions. Saccharin in the urine and feces samples was extracted into ether and separated by HPLC (18). Daily saccharin intake was estimated based on the diet consumption and taking into consideration water content in the chemicals. Feces of rats given any form of saccharin was increased in water content. Especially, Ca-S and Acid-S treated rats showed marked diarrhea and saccharin was excreted in the feces more than in the urine. However, saccharin concentration in the urine was similar in rats fed the different forms of saccharin.

nsda
NATIONAL SOFT DRINK ASSOCIATION 1101 SIXTEENTH STREET, NORTHWEST • WASHINGTON, D.C. 20036 • (202) 463-6732

April 16, 1985

The Honorable Orrin Hatch
Chairman, Senate Labor and Human
 Resource Committee
United States Senate
Washington, D.C. 20510

Dear Mr. Chairman:

During my testimony at the Committee's April 2, 1985 hearing on S. 484, a copy of an internal draft NSDA document pertaining to the FDA approval for the use of aspartame in carbonated beverages was made part of the hearing record by Senator Metzenbaum. NSDA does not object to the inclusion of that document in the record but would like to assure that it be considered in proper context. NSDA therefore respectfully requests that this letter be included in the hearing record along with the subject document.

NSDA would like to affirm at the outset that the soft drink industry is convinced that aspartame is safe for use in soft drinks; any previously expressed reservations have been adequately resolved. We are also satisfied that FDA followed appropriate regulatory procedures in authorizing aspartame use in soft drinks.

It should be emphasized that the document to which Senator Metzenbaum referred was in fact an internal NSDA draft document generated to facilitate evaluation of issues by our member companies. It was not submitted to the FDA and does not reflect NSDA's views on aspartame.

The draft document was part of a thorough NSDA evaluation which convinced us of aspartame's safety for use in sweetening soft drinks. Having made that evaluation, we became satisfied that there was no reason to submit the draft document to FDA.

The draft document was drafted by our attorneys in the legal format prescribed for submission to FDA, rather than in a less formal format, because of the short time period allowed by law for filing such objections and to permit consideration of the issues in the proper legal context. That approach indeed permitted the most thorough possible evaluation of potential issues by our members prior to the statutory deadline for submitting objections.

Previous experience with sweeteners (i.e., cyclamate and saccharin) together with the regulatory history of aspartame between 1974 and 1983, had understandably made the soft drink industry quite sensitive concerning the approval of a new sweetener. Because of that sensitivity, we felt obligated not only to satisfy ourselves concerning the safety of aspartame but also to satisfy ourselves that any objections raised subsequent to approval could be readily resolved. The subject draft document was a part of the evaluation process which enabled us to be satisfied on both counts. That process, as noted, led us to the conclusion of the safety of aspartame for use in soft drinks.

Sincerely,

Howard R. Roberts

Howard R. Roberts, Ph.D.

clr

The **Chairman**. Well, thank you so much.

Dr. Jacobson, saccharin feeding studies have not shown any increase in tumor production in mice, hamsters, or guinea pigs, or in female rats.

Now, if we are going to extrapolate, why is it not as reasonable to infer the safety of saccharin based on those results than the peril of saccharin based on high feed levels in just one sex of one species, in this case the rat?

Mr. **Jacobson**. Well, I think you have to realize the very narrowness of the animal studies.

Chemicals, potential food additives, are tested on single highly inbred strains of particular animals. These animals are carefully protected from pollutants, drugs, a whole range of environmental pollutants that might interact and increase the risk of cancer.

Furthermore, the animals, unlike human beings, are protected from diseases. They don't suffer malnutrition; they are fed an extremely good diet. They don't have allergies, alcoholism, or a whole range of infectious diseases, any of which could increase the risk.

So the tests, I think, give a bare indication of what the effect on humans might be, and we have to interpret the animal studies extremely conservatively, recognizing that just because it didn't cause cancer in one single strain of mouse —they did not test all the strains of mice—and on extremely healthy animals, and usually chemicals would affect the most susceptible members of a population, not the healthiest, we should respect any indication that a chemical causes a cancer.

The fact that the tumors are not labeled with their cause makes it easy to think just in terms of statistics and forget that these tumors cause tremendous devastation to a family as well as to the individual.

In the case of sulfites, the chemical added to salad bars, we see that the public is extremely upset over any deaths whatsoever. Sulfites have killed five people. The damage done by saccharin is more invisible, and we have to really imagine in our minds the damage that saccharin is probably causing and view in our minds those cancer deaths, and I think we do have to consider the animal studies and give great credence to any indication of cancer.

The Chairman. I don't think any scientist who has testified today has gone as far as you, but I understand where you are coming from.

Let me ask one other question. I am going to submit questions in writing to you as well as to Dr. Roberts. I will ask a couple of questions of Dr. Roberts.

Has the Center for Science in the Public Interest petitioned FDA to review the saccharin labeling situation? Have you asked the FDA to review it and do something about it? If not, isn't it premature to come to Congress before FDA acts?

Mr. JACOBSON. I don't believe we have, but our experience with FDA is that sometimes FDA will approve particular matters, but the Secretary of HHS kills it or OMB kills it, as was demonstrated last week with sulfite labeling or with red dye number 3, which came up before. FDA has proposed banning it, but that got killed at the Secretary's office.

Congressional action could bypass a lot of agency foot-dragging.

The CHAIRMAN. Dr. Roberts, what does the overall usage of saccharin look like for all types of uses—foods, drugs, cosmetics, et cetera? Is it increasing, is it decreasing, or is it staying about the same? What are the implications of any trends in usage that you see?

Mr. ROBERTS. At present, the trend is downward. There have been a number of switches including major diet soft drinks, to 100-percent aspartame, and that is decreasing the use of saccharin. The projections I have seen for 1985 and beyond would indicate a decrease.

Now, if one has some concern about saccharin consumption, that decreased trend, of course, would be a very favorable kind of development.

The CHAIRMAN. How does the soft drink industry view a possible requirement discussed earlier for the quantitative labeling of aspartame? What is your viewpoint with regard to that?

Mr. ROBERTS. Well, one thing I would like to point out, Senator Hatch, is that our association provides a variety of information on soft drinks to the public. I have brought along some of our pamphlets, and I would like to submit these for the record.

The CHAIRMAN. Without objection, we will put them in the record.

[Note: Due to printing limitations the pamphlets referred to were retained in the files of the committee.]

[Responses to questions submitted for the record follows:]

Questions for Panel Four (Ronald Arky, Michael Jacobson, Howard Roberts)

Submitted by Senator Grassley

You noted in your statement that children and women in child-bearing years may be at a "higher than normal risk." What is the practical meaning of "higher than normal risk?" Would you advocate label warnings addressed to these groups?

Answer:

The assertion in Dr. Arky's statement that:

> Subjects who may be at a higher than normal risk from artificial sweetener ingestion include children and women in the child-bearing years, because ingestion may be greater than in other groups.

is a generic statement relating relative risk to exposure. For any given hazard the risk would normally be expected to increase as the exposure increased. If there were a risk to humans from saccharin consumption and if children and young women consumed more saccharin than others, they would be at greater risk than others. However, there is a growing scientific consensus that saccharin is not the kind of substance that is classically thought of as a carcinogen and that tumors occur in the male rat only as a consequence of abnormal physiological conditions that result only from high doses and that are not relevant to humans. That consensus is bolstered by steadily accumulating epidemiological evidence that saccharin has not increased the risk of cancer in humans. There is thus no justification for special warning statements on saccharin-containing products for the general population or any sub-population.

Question for Dr. Roberts

Submitted by Senator Grassley

Dr. Roberts, do we need a three-year extension of this ban? What is the likelihood that we will get some definitive conclusions with respect to saccharin -- safely within, say, the next one or two years?

Answer:

As discussed in my detailed statement submitted for the record, a three year extension of the moratorium on regulatory action against saccharin is justified from several points of view. First, scientific evidence from both animal and epidemiology studies support the conclusion of an absence of any significant human risk from the ingestion of saccharin. Thus, there is not any public health justification for an abbreviated extension period. Further, the scientific research which is seeking an explanation of the apparently unique effects that occur only at high doses and only in male rats is complex and cannot necessarily be expected to yield completely satisfactory answers in a short period of time. In addition, the approval of other sweeteners, such as cyclamate which could be used in some of the same applications as saccharin, is not expected in the near future. Therefore, for many uses saccharin will remain the only suitable non-caloric sweetener for the time being. Finally, it is noted that modernization of food safety law, along lines which would permit the rational regulation of saccharin, is also a complex process the completion of which is not necessarily assured in the immediate future.

Mr. **Roberts**. We take great pains and devote a lot of effort to put forth information on the ingredients in soft drinks. We have a brochure called "What's in Soft Drinks?" that we periodically put out. We are in the process of revising that right now. That brochure lists, by type, the aspartame content of the different types of soft drinks.

We like people to have this information, so we have no objection whatsoever to its release, and in addition, we try to provide additional information by putting out associated kinds of brochures.

The question of labeling, I think, brings up a different aspect of the problem. There is more than one way to convey product information to consumers other than by labeling, and I think this kind of information is very useful.

What one might decide relative to a specific labeling proposal, I think, would depend on the content of that proposal. There already is some problem with the amount of information on some food labels, and whereas we want to convey usable information to consumers, we would have to be very careful in any given situation in how we put that information on a product label, but with respect to conveying it in other ways, we have no objection. We like people to know.

The **Chairman**. All right. Senator Metzenbaum.

Senator **Metzenbaum**. Mr. Jacobson, you mentioned in your testimony you do not think that a 3-year extension is a good idea. Do you believe that there should be an extension, and if so, for what period of time?

Mr. **Jacobson**. Well, frankly, I think an extension is inevitable. I would prefer that saccharin be banned. I think there are a lot of things going on in the artificial sweetener world right now. Cyclamates may be approved. Acesulfame K may be approved. The clinical studies on aspartame may be done in the next number of months.

Senator **Metzenbaum**. But what I am asking you is——

Mr. **Jacobson**. And I think a 1-year extension would be better than a 3-year extension.

Senator **Metzenbaum**. If this committee and the Senate could bring about, Congress could bring about, the labeling of vending machines, would you not think that that was a major step forward without the need to insist that it be in every advertisement, the warning?

Mr. **Jacobson**. It would certainly be a step forward.

Senator **Metzenbaum**. Dr. Roberts, how long have you been the—what are you, the executive director of the National Soft Drink Association?

Mr. **Roberts**. No; I am vice president for science and technology.

Senator **Metzenbaum**. Were you aware of the fact that there was prepared on behalf of the National Soft Drink Association objections to a final rule permitting the use of aspartame in carbonated beverages, in carbonated beverage syrup bases, and a request for a hearing on the objections, and it was prepared by Stuart M. Pape of Patton, Boggs, & Blow, and Thomas A. Daly, general counsel, attorneys for the National Soft Drink Association? Are you aware of that particular document that was never filed?

Mr. **Roberts**. That document was not an objection. That was a draft internal document, Senator, and yes, I am aware of it.

Senator **Metzenbaum**. Well, they just called it, said at the top of it on the draft, "Before the U.S. Department of Health and Human Services, Food and Drug Administration," and they called it Objections of the National Soft Drink Association to a Final Rule Permitting the Use of Aspartame in Carbonated Beverages, et cetera, and they gave the docket number, 82F-0305, and they referred to it as Aspartame Food Additive for Direct Addition to Human Food, 48 Federal Register 31376, July 8, 1983, and had the lawyers' names on it. And you say that was just an internal document?

Mr. **Roberts**. It was a draft internal document, Senator. It was drafted in the form which could have been submitted had the decision to do so been made. If we were going to submit such an objection, there is a prescribed format, as you have so carefully laid out, in the detail that would have been used. If one is going to draft such a document, one drafts it in the form in which it would be submitted.

Senator **Metzenbaum**. Mr. Chairman, I think I would like to ask that a copy of this document be submitted for the record because it does indicate that at one point in the history of the National Soft Drink Association, they had very strong objections and gave some very persuasive reasons as to why aspartame should not be legally permitted to be used in carbonated beverages.

The **Chairman**. Without objection, we will put it in the record.

[The document referred to above follows:]

DRAFT

BEFORE THE
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

OBJECTIONS OF THE NATIONAL SOFT DRINK ASSOCIATION TO A FINAL RULE PERMITTING THE USE OF ASPARTAME IN CARBONATED BEVERAGES AND CARBONATED BEVERAGE SYRUP BASES AND A REQUEST FOR A HEARING ON THE OBJECTIONS.

Aspartame; Food Additives For Direct Addition To Human Food; 48 *Fed. Reg.* 31376 (July 8, 1983).	Docket No. 82F-0305

Stuart M. Pape
Patton, Boggs & Blow
2550 M Street, N.W.
Washington, D.C. 20037

Thomas A. Daly
General Counsel
National Soft Drink Association
1101 16th Street, N.W.
Washington, D.C. 20036

Attorneys for the National
Soft Drink Association

Date: August 8, 1983

OBJECTIONS OF THE NATIONAL SOFT DRINK ASSOCIATION TO THE ISSUANCE BY THE FOOD AND DRUG ADMINISTRATION OF A REGULATION (21 C.F.R. § 172.804) TO AUTHORIZE THE USE OF ASPARTAME IN CARBONATED BEVERAGES AND CARBONATED BEVERAGE BASES.

In the Federal Register of July 8, 1983 (48 Fed. Reg. 31376), the Food and Drug Administration ("FDA") issued a regulation amending section 172.804 of its regulations, 21 C.F.R. § 172.804, to authorize the use of aspartame in carbonated beverages and carbonated beverage bases (collectively referred to as "soft drinks"). This action was taken in response to a food additive petition (FAP 2A3661) filed on October 15, 1982 by the Searle Research and Development Division of the G.D. Searle Co. ("Searle").

In these objections, NSDA demonstrates that there exist genuine and substantial issues of fact material to FDA's amendment of its regulations to permit aspartame use in soft drinks. Specifically, Searle has not met its burdens under section 409 of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 348 ("FDC Act") to demonstrate that aspartame is safe and functional for use in soft drinks. NSDA therefore objects to the Commissioner's order amending 21 C.F.R. § 172.804 and requests that a hearing as provided under section 409(f) of the FDC Act, 21 U.S.C. § 348(f) be convened.

NSDA is a party that is, within the meaning of section 409(f)(1) of the FDC Act, 21 U.S.C. § 348(f)(1), "adversely affected" by the issuance of the regulation authorizing the use of aspartame ("APM") in soft drinks. As the national trade association representing the soft drink industry in this country, NSDA's member soft drink manufacturers and soft drink franchisers are directly and immediately affected by the issuance of a regulation which authorizes the use of a new sweetener in its products. Approximately seventy-six percent of the nation's 1600 soft drink manufacturers are active members of the Association. These members account for more than ninety percent of the soft drink production in this country. In addition, the vast majority of soft drink franchisers which manufacturer the concentrates and syrups from which soft drinks are made are associate members of the Association.

II. Summary of Basis for The Objections

[TO BE ADDED]

DRAFT: 7/28/83

OBJECTION ONE: SEARLE HAS NOT DEMONSTRATED TO A REASONABLE CERTAINTY THAT ASPARTAME AND ITS DEGRADATION PRODUCTS ARE SAFE FOR USE IN SOFT DRINKS, WITHOUT QUANTITATIVE LIMITATION, UNDER TEMPERATURE CONDITIONS LIKELY TO PREVAIL IN THE UNITED STATES.

Summary of Basis for Objection

Aspartame is inherently, markedly and uniquely unstable in aqueous media. In a liquid, such as a soft drink, APM will degrade as a function of temperature and pH. Higher temperatures and more acidic liquids increase the rate of degradation. Higher temperatures may also affect the degradation products which are formed. Given the circumstance of APM's unusual instability, reliable and comprehensive analyses of APM's degradation in soft drinks -- both as to the rate of degradation (and the subsequent loss of sweetness) and to the confirmed identification of the major degradation products -- is crucial to establish the safety of the use of APM. Without adequate identification of APM's significant decomposition products, it is not possible to find, to a reasonable certainty, that APM is safe. The data and information submitted by Searle in support of its petition to amend 21 C.F.R. § 172.804 to permit APM use in soft drinks, however, do not demonstrate that APM is safe for use in soft drinks. These data are insufficient to establish safety because the petition lacks comprehensive, reliable and accurate analytical data on APM and the products of its decomposition under the temperature conditions to which soft drinks are known to be exposed in the United States.

In order to establish that a food additive such as APM, which is known to degrade rapidly, especially in liquid systems, is safe for use in soft drinks, the petitioner must:

(1) use suitable and reliable analytical methods which are available to identify and quantify the principal products of the degradation of the additive;

(2) conduct its analyses of the additive in accordance with established procedures for such studies; and

(3) conduct its analyses under conditions which reasonably approximate actual conditions of use or which permit reliable extrapolations to actual conditions of use.

Searle has not satisfied these requirements.

Factual Basis for Objection One

1. Aspartame's Major Decomposition Products In Soft Drinks Have Not Been Reliably and Comprehensively Identified.

(a) Analysis of APM Degradation Products in Soft Drinks Was Not Conducted With Sutiable and Reliable Analytical Methods.

Searle analyzed soft drinks sweetened with APM for six substances: APM, diketopiperazine (DKP), aspartylphenylalanine (A), phenylalanine (PHE), phenylalanine methyl ester (PM) and beta-aspartame (beta-APM).*/ (Searle FAP at 13) Only in the cases of APM and DKP did Searle use high pressure liquid chromotography (HPLC). For the other four known principal breakdown products, Searle used thin-layer chromotography (TLC).

HPLC is a far superior analytical method relative to TLC (cites) and numerous HPLC methods exist for the detection and quantification of amino acids (cites. Searle's choice of TLC over HPLC adversely affected the quality and type of analytical data generated on APM and its decomposition products in soft drinks. The unfortunate and inexplicable choice**/ of an inferior analytical technique, when superior and recognized methods are available, has resulted in inadequate characterization of APM's decomposition products.

---

*/ The importance of comprehensive and reliable analyses of APM's decomposition products is demonstrated by the fact that based on the chemical structure of APM, one would not expect PM or beta-APM to be degradation products. Indeed, initially Searle did not look for either one. Other unexpected decomposition products of unproven safety could, of course, also be present when APM degrades.

**/ The availability of HPLC to detect and quantify APM's decomposition products is demonstrated by, among other things, a paper presented in 19__ by three representatives of Searle. (LeVon, Mazur and Ripper, "Aspartame (APM) as a Sweetener In Carbonated Soft Drinks") (Appendix______). In that paper, Searle stated that HPLC was currently used to detect APM, DKP and AP and PHE. Nevertheless, the petition does not contain HPLC-generated data for AP or PHE.

HPLC is a practicable, well-accepted analytical method*/ which is commonly-employed by FDA. When the safety and suitability for use of a food additive such as APM with an acknowledged degradation problem (and anticipated high consumption) is under evaluation, HPLC is clearly the analytical method of choice.

TLC, on the other hand, produces good qualitative results, but is, at best, only semi-quantitative, since the quantification used is based on visual comparisons of spot sizes and intensities. (cite) Indeed, Searle itself has acknowledged the inadequacy of the analytical method that it chose, when it described, in the petition, the quantity of degradation products identified using TLC as "estimates." (cite)

The inappropriateness of using TLC as a principal analytical method is compounded by the fact that the values of APM degradation products being measured are close to the limits of detection of the method (cite).**/

---

*/ Section 171.1(c) of the agency's regulations, 21 C.F.R. § 171.1(c), requires that an analytical method for detection of a food additive and substances formed in or on food because of its use be practicable and one which "can be applied with consistent results by any properly equipped and trained laboratory personnel. HPLC is clearly such a method.

**/ FN w/examples.

Thus, the values purportedly obtained by the TLC method cannot be considered to be very precise. Finally, an important decomposition product of APM, aspartic acid (AA) cannot be detected at all using TLC.

In short, for reasons which are not apparent, the petitioner chose to use a semi-quantitative analytical method to analyze for numerous major APM breakdown products close to the limits of detection, when that method is not the best method available. The quality of the analytical data presented are, therefore, substantially inferior to those which could have reasonably been obtained.

(b) The Searle Analyses for APM Decomposition Products Are Deficient.

Aside from its choice of TLC over HPLC, the analyses conducted by the petitioner to identify and quantify the breakdown products of APM in soft drinks are plagued by numerous significant deficiencies which result in clear and unmistakable inadequacies in the detection and quantification of the major decomposition products of APM in soft drinks. In the face of these deficiencies, Searle has not reasonably identified substances formed in soft drinks because of the use of APM, as required under section 409(c)(5)(A) of the FDC Act, 21 U.S.C. § 348(c)(5)(A). The safety of this use of APM cannot be said to have been shown to a reasonable certainty in the face of these inadequacies.

There are at least six significant deficiencies in the HPLC analyses undertaken by Searle to identify and quantify APM and DKP in soft drinks:

(a) The standards for use of HPLC to detect APM and DKP were prepared in buffered aqueous solutions. A far better technique would have been to prepare the standards using beverage matrices. The use of beverage matrices would have reduced the danger of interfering compounds coeluting with the compound of interest.

(b) Searle does not appear to have submitted to FDA to HPLC chromatograms of the blanks (unsweetened beverages); without these chromatograms, the results obtained in sweetened beverages cannot be evaluated.

(c) The chromatograms of the beverages which were submitted by Searle contain peaks which can cause difficulties with quantification. For example, the DKP in the root beer chromatograms is badly overlapped by another peak.

(d) No recovery data for DKP were presented and the precision of the DKP concentrations was only determined for standard solutions.

(e) The purity of the initial APM was not established, although it can contain at least five percent impurities, as calculated from the zero time values in Searle's studies.

(f) Searle analyzed only single bottles at any given time and temperature. This aspect of the study design fails to account for anticipated bottle-to-bottle variations. Single bottle analytical data cannot, under any circumstances, amount to a comprehensive and reliable characterization of the decomposition products of an additive with a well-known instability problem.

Likewise, the TLC analyses are deficient (these deficiencies are in addition to the inherent limitations of the TLC method):

(a) Standards for the TLC analyses were prepared in distilled water. As in the case of the HPLC analyses, the better technique would have been to prepare them in beverage matrices.

(b) Searle did not submit (and apparently did not attempt) any recovery or precision data for its TLC analyses.

(c) In the TLC analyses, only single aliquots of single bottles were analyzed at any given time and temperature, thus rendering the putative quantitative results inherently unreliable.

(d) Measurable levels of beta-APM and PM may have existed in the starting material, but were not quantified at the beginning of the analyses (presumably because they were unexpected decomposition products). Moreover, it is unclear from Searle's data how the spots on the TLC plates were identified. If, as appears to be the case, identification was based solely on the comparison of R_f values, the identifications can only be called tentative. Confirmation of the identifications by spectroscopic methods should have been undertaken. The failure to confirm these identifications undermines many of the major assumptions made by Searle throughout its analytical studies.

Collectively, the extensive deficiencies in the stability studies conducted by Searle to demonstrate that APM and its degradation products are safe in soft drinks intended to be sold in the United States, render those studies inadequate and unreliable. It is not possible on the basis of these studies to conclude that the petitioner has demonstrated that, notwithstanding its inherent instability, APM is safe for use in soft drinks. The failure of proof by Searle is even more evident, as is shown in the following section of these objections, when one considers the extent to which the decomposition products of APM in soft drinks are not known or identified.

(c) APM Decomposes Extensively in Soft Drinks Under Moderate Conditions, But Searle's Data Fail to Identify Adequately the Decomposition Products.

Notwithstanding the multiple and serious deficiencies in the stability studies conducted on APM in soft drinks, one conclusion does emerge: under moderate conditions, extensive decomposition of APM may occur in soft drinks. Moreover, a substantial portion of the decomposition products are not known. APM cannot be considered to be shown to be safe for use in soft drinks when the results of its known decomposition phenomenon -- marked breakdown in liquid beverages -- are not well identified.

For example, in the Searle studies, a cola beverage was kept at 30°C (86°F) for 40 weeks. (cite) In analyses conducted at that time, only fifty (50) percent (weight basis) of the original starting material was found.*/

---

*/ This figure is derived as follows from Searle data: 13% AOM, 21% DKP, 3% AP, 8% PHE, and 5% PM.

Even if one accepts one of Searle's main assumptions about APM decomposition in soft drinks -- that is, that aspartic acid (AA) is formed in amounts equal to the PHE and PM (mole basis) and that methanol is formed in amounts equal to the DKP, AP and PHE (mole basis) (cite) -- the precent recovery of the original material is only increased to sixty-four (64) percent.*/ Thus, even when viewed most favorably, the analyses fail to account for over one-third of the original material.

This startling deficiency in the stability studies is further demonstrated by this table, also drawn from Searle data of beverages stored at 30°C (86°F), which illustrates the material balances obtained:**/

		26 Weeks		40 Weeks	
odel everage	pH	%APM Remaining	% Unaccounted For	%APM Remaining	% Unaccounted For
oot Beer	4.5	63	23	50	15
emon-Lime	3.6	51	22	35	26
range	3.3	41	32	23	39
ola	3.1	24	23	13	35

---

*/ The increase comes from 10% AA and 4% methanol.

**/ A material balance accounts for the quality of the starting material, the quantity of identified decomposition products (or by-products, reaction products etc.) and the quantity of unknown material. Because of the inadequacies in the analyses documented in section____ above, the figures in this table may be inaccurate. Nevertheless, the discrepancies in the material balance raise the possibility of significant unknown decomposition products.

The inability to account for as much as thirty-nine (39) percent of APM's decomposition products is significant. With such a high unknown factor, judgments about the safety of APM in soft drinks cannot be made confidently. Possible explanations for, and speculation about, the material balance discrepancies abound: secondary reactions may be occurring (possibly with the flavor components in the beverages); additional, but unidentified decomposition products may exist (as occurred in the case of Pm and beta-APM); or the inaccuracy and inadequacies of the analytical methods may account for the gaps in the data. No explanation for the discrepencies in material balances -- that is, for the high percentage of unknown material -- can, however, be supported on the basis of the data submitted by Searle. The significance of the unknown decomposition products simply cannot be determined in the absence of complete, careful and reliable analyses -- analyses which are not currently available because the petitioner failed to conduct or submit them.*/

---

*/ A tempting, but unsatisfactory, resolution of the material balance discrepancy is to assume that the safety of the decomposition products were determined in the chronic studies in laboratory animals which Searle conducted. This putative resolution does not hold, however, because these degradation products would not have undergone testing, since the APM in the feeding regimen was in freshly prepared doses.

2. Searle Has Not Characterized The Decomposition Products of APM in Soft Drinks Under Temperature Conditions To Which The Beverages Are Likely To Be Exposed In the United States.

A suitable assessment of the stability of APM in soft drinks can be conducted. Such an assessment would necessarily involve the use of sample beverages in a variety of flavors and varying pH, and, most importantly, involve exposure of the beverages to temperature conditions which approximate those which are reasonably expected to occur in practice (or under conditions which permit reasonable projections to be made to actual conditions)*/ Unless the sample APM-sweetened beverages are exposed to realistic temperature conditions, the temperature-sensitive degradation characteristics of APM, and in particular its potentially significant decomposition products, cannot be known. The data submitted by Searle are not derived from appropriate test conditions. Judgments about the extent of APM instability and its degradation products in soft drinks under actual conditions of use cannot, therefore, be inferred from the limited laboratory data.

---

*/ The use of exaggerated, but realistic, test conditions is a routine facet of testing to establish the safety of food additives. For example, pursuant to FDA guidelines, extraction testing to detect and quantify migrants from packaging materials is required to be conducted under temperatures and for time periods which are known to exceed actual conditions of use.

To assess APM's instability in soft drinks, Searle exposed bottles of ready-to-drink beverages in four flavors (cola, root beer, lemon-lime and orange) to consistent temperatures of 55°, 40, 30, 20 and 5°C.*/ According to Searle's petition, "[I]n each flavor a loss of APM occurred with the rate of degradation directly related to the stroage temperature for the carbonated beverages. The rate of APM loss from beverages was pH dependent." Moreover, Searle noted that "as the temperature increases, the rate of degradation becomes more pronounced."**/ Some of the effects on APM degradation in soft drinks are illustrated in a table in the Searle petition.***/ In that table, for example, after 20 weeks at 30°C (86°F), a beverage with a pH between 2.5 and 3.0, contained less than 40 percent of the original amount of APM. For beverages with similar pH, but kept at 40°C (104°F) for 20 weeks, less than ten percent of the original APM remained. Less pronounced degradation is seen at higher pH and/or at lower temperatures.

---

*/ Similar, but equally limited studies were conducted using carbonated beverage bases (syrups).

**/ In the preamble to the regulation authorizing APM use in soft drinks,FDA itself acknowledged this phenomenon: "At temperatures above 30°C (86°F) the stability drops off markedly." 48 Fed. Reg. at 31377. As shown below, soft drinks are frequently exposed to temperatures well in excess of 30°C (86°F).

***/ Searle FAP at 14, Fig. 3.

Although these stability tests shown significant degradation of APM at consistent temepratures over relatively short time periods, they shed virtually no light on the probable degradation rate and products for soft drinks exposed to a *variety* of temperatures -- including temperatures *higher* than any used in Searle's studies -- during storage, handling, sale and use, temperatures which are known to occur and to which soft drinks are known to be exposed. Without stability studies conducted under such conditions, APM cannot be said to be appropriately stable in soft drinks, nor can its degradation products be considered to be adequately identified (assuming that analytical techniques were used which would yield complete and reliable results) nor can it be considered to have been shown to be safe.

The range of temperature conditions to which soft drinks are exposed during the summer months in the southern United States*/ is illustrated by a study conducted by the Coca-Cola Company's Corporate Packaging Department in 1976 and submitted to the Consumer Product Safety Commission.*/ That study shows that during the summer months, soft drinks are often exposed to relatively high temperatures for certain time periods in the course of distribution from the bottling plant to the consumer. High temperatures do, of course, routinely occur in much of the United States, including the southern regions; conditions of storage and distribution for soft drinks can elevate these temperatures significantly.

---

*/ High summer temperatures are by no means limited to the southern states. During the period July 10 to July 24, 1983, for example, St. Louis, Missouri experienced 14 consecutive days of temperatures over 90 °F, and 10 days of temperatures of 95°F or greater. During the same period, Louisville, Kentucky experienced similar temperatures.

In summary, the study assessed: (1) warehouse temperatures in Marietta, Georgia and Wichita Falls, Texas; (2) route truck temperatures in Wichita Falls; (3) full sun and outside ambient temperatures in Wichita Falls;**/ and (4) parked car temperatures in Atlanta, Georgia and Wichita Falls. Each of these test environments is known to occur in practice and the tests were performed under actual, as opposed to laboratory, conditions.

---

*/ Study cite. A full description of this study is contained in Appendix_______.

**/ Full sun exposure occurs, for example, when a service station runs a promotion in which cases of the beverages are stacked in front of the station in full view of passing moterists and therefore often in direct sunlight.

Several significant conclusions can be drawn from this study. First, in those situations where the bottled beverage is heated only by conduction from the surrounding air (shaded location in a warehouse or in an automobile trunk parked indoors) the ratio of product temperature to the temperature of the surrounding air would be 0.92 to 0.94. In enclosed environments exposed to sunlight, however, ratios much greater than one would be expected. For example, a ratio of product temperature to air temperature of 1.45 was found for a test car parked in full sunlight. In other situations where sunlight was a direct heating factor (e.g., open air service station promotions or open bay delivery trucks) typical ratios were 1.10 to 1.15.

The effects of these ratios on product temperature are demonstrated by using summer temperatures for Phoenix, Arizona, where the average daily high in July is 40°C (104°F). During July in Phoenix, a soft drink in full sunlight could reach a temperature of 49°C (120°F) (104° x. 1.15). The same product in a car parked in full sunlight could reach 66°C (151°F) (104°F x. 1.45)*/; soft drinks in a warehouse with an ambient temperature of 110° could reach temperatures of 38°C (101°F) to 39°C (103°F) (0.92 - 0.94 x. 110°F).

---

*/ This temperature exceeds by 11°C (20°F) the highest temperature used in Searle's stability studies. In those studies, after less than four weeks, beverages stored at 55°C (131°F) contained less than twenty (20) percent of the original amount of APM. (Searle FAP at 83)

Overall, the study, considered together with representative historical temperature data (Appendix________) show that soft drinks will frequently be exposed to temperatures of 32°C (90°F) to 49°C (120°F). In some cases product temperatures as high as 66°C (151°F) (especially in the southwestern United States) can be reached.

The effects of these high product temperatures on APM degradation and the formation of degradation products, and the effects of temperature variation (for example, soft drinks displayed at a service station may reach temperatures of 49°C (120°F) for most of the afternoon, drop in temperature overnight, and heat up again during the following day) cannot be determined from the data submitted by Searle to the FDA.

What those data do suggest, however, is that significant APM degradation at high temperatures occurs within a short period of time. For example, in Searle's stability tests, an orange beverage held at 40°C (104°F) (average daily high for Phoenix during July) for eight weeks, contained only fifty (50) percent of the original amount of APM. A cola beverage held under the same conditions contained only forty (40) percent of the original APM amount. And beverages exposed to higher temperatures degrade even more rapidly. And, of course, because of the temperature elevation ratios, product temperatures could easily be much higher during actual conditions than the stable temperatures used in the Searle laboratory studies.

Thus, it is known that APM will degrade rapidly at high temperatures, including temperatures to which soft drinks are known to be exposed intermittently during the summer. What is now known, although the FDC Act requires the proponent of use to demonstrate it, is what effects of degradation occur by virtue of exposure to these temperatures. More specifically, to demonstrate that APM is safe for use in soft drinks, the petitioner must reasonably identify what degradation products are formed under those conditions. Ultimately, of course, the safety of the major degradation products must be determined. Under the FDC Act, the data needed to make that determination -- reliable and competent data -- must be provided by the petitioner.

OBJECTION TWO: SEARLE HAS NOT DEMONSTRATED THAT APM USE IN SOFT DRINKS WILL NOT ADULTERATE THE BEVERAGES UNDER SECTION 402(a)(3) OF THE FDC ACT.

Summary of Basis for Objection

As discussed in section_____ above, it is well established that the petitioner for issuance of a regulation authorizing the use of a food additive bears the burden of proving, through reliable and competent data, each element of the criteria set forth in section 409 of the FDC Act, 21 U.S.C. § 348, for issuance of a food additive regulation. The present record does not contain data which demonstrate that the use of APM in soft drinks will not result in the adulteration of the beverages under section 402(a)(3) of the FDC Act, 21 U.S.C. § 342(a)(3), which provides that a food is adulterated if it contains, in whole or in part, ". . . a decomposed substance or if it is otherwise unfit for food." Indeed, the present record strongly suggests that the rapid degradation of APM in soft drinks and the consequent loss of sweetness may well result, under certain actual time and temperature conditions, in products which would be adulterated under section 402. Without data which demonstrate that APM-sweetened beverages will not be adulterated under section 402(a)(3), Searle has not met its burden of proof under section 409(c)(3)(B) of the FDC Act, 21 U.S.C. § 348(c)(3)(B).

Factual Basis for Objection Two

The marked and rapid decomposition of APM in soft drinks under temperaturesknown to prevail is apparent from data in the present record and discussed above in these objections. Those data show that it is reasonable to expect APM to decompose in soft drinks sufficiently rapidly under current handling and distribution procedures to adversely affect product quality and taste.*/

It is well-established under section 402(a)(3), that a food which contains a decomposed substance (i.e., the decomposition products of APM which, Searle's data show, can readily exceed the quantity of APM itself in a short time) -- especially where the decomposition has adversely affected product quality or made the product unpalatable -- is adulterated and subject to seizure. (cites). It is quite clear, for example, that FDA would consider beverages which had lost substantial sweetness because of APM decomposition and which were therefore not palatable, to be adulterated under section 402(a)(3). The record is devoid, however, of evidence which demonstrate that APM used to sweeten soft drinks will not, under reasonably anticipated conditions of use, in fact cause the products to be adulterated. Without such evidence Searle has not met the burden imposed under section 409(c)(3)(B).

---

*/ FDA acknowledges this distinct possibility when it states its "belief" that changes in these procedures will avoid the problem. Section 409(c)(3)(B) does not contemplate that a "belief" in unspecified, but fundamental, changes in industry practice are adequate to assure that widespread use of a food additive will not adulterate the food.

[This objection will be expanded.]

OBJECTION THREE: SEARLE HAS NOT DEMONSTRATED THAT APM IS FUNCTIONAL FOR USE IN SOFT DRINKS UNDER TEMPERATURE CONDITIONS LIKELY TO PREVAIL IN THE UNITED STATES.

Summary of Basis for Objection

In addition to data intended to assess the stability of APM in soft drinks, Searle's petition for use of APM in soft drinks contains data intended to show that APM is functional in the beverages, *i.e.*, that it achieves and retains the intended technical effect (sweetening) under the conditions of use reasonably anticipated to occur. Searle has not demonstrated that APM is functional in soft drinks because its data show a significant loss of sweetness at temperatures to which soft drinks are known to be exposed and within the range of time periods between bottling and projected consumption. The functionality of an additive cannot be considered to have been demonstrated if significant loss of its intended technical effect (because of temperature and pH dependent degradation) may occur under reasonably anticipated conditions of handling, storage and use.

Factual Basis for Objection Three

To evaluate the functionality of APM, Searle conducted "sensory evaluation" tests which used consumer taste panels to assess "perceived sweetness" (cola, beverages only) and "overall liking" (or "acceptance") (all flavors) over time periods up to 52 weeks and at three temperatures: 5°C (41°F), 20°C (68°F) and 30°C (86°F). Beverages sweetened with APM only (5,20 and 30°C) and APM with saccharin (20°C) were tested; beverages sweetened with sucrose (______°C) and saccharin (________°C) were used as references. The beverages were rated at different time periods by the panelists.*/

Although no temperature used in Searle's sensory evaluation tests approached the actual product temperatures which soft drinks will reach (see section_____above), significant loss of sweetening and overall liking occurred for beverages sweetened with APM only within extraordinarily short time periods. For example, APM-sweetened cola beverages stored at 30°C (86°F) received an overall liking score of less than 20 on a 0-100 scale after only 20 weeks (after 20 weeks the product was apparently unpalatable, since Searle did not present sensory evaluation data beyond this time). For an orange beverage, overall likness after 20 weeks at 30°C (86°F) approached 5 (on a nine point hedonic scale), the "neither like nor dislike" or mean rating. Again, sensory evaluations were apparently not conducted beyond 20 weeks.

---

*/ Fn. stating rating periods.

Searle's characterization of the results of the sensory evaluation tests avoids the clear implication of those tests: that APM has not been shown to retain sufficient sweetness at temperatures which are known to occur for APM-sweetened beverages to retain an acceptable "overall liking" rating. Instead, Searle emphasizes an interesting, but legally irrelevant finding: that APM sweetened beverages tested after holding at relatively low temperatures were preferred to beverages sweetened with alternative sweeteners. This characterization misses the statutory purpose for which the studies were undertaken, that is, to demonstrate that APM is a functional sweetener in soft drinks.

Of particular importance is the fact that Searle's sensory evaluation tests do not explore the effects on either sweetness or overall likness of APM-sweetened beverages exposed, either consistently or intermittently, to the higher temperatures which prevail in much of the United States. What is the effect on these two measures, for example, of product temperatures of 100 to 120°F? Is the degradation greatly accelerated and the overall liking therefore diminished in even shorter time periods? Will APM-sweetened beverages stored in warehouses and carried on open route trucks or stored in warehouses and displayed in open air service station promotions in the southern states be acceptable when the consumer attempts to consume them several weeks later? Is APM a functional sweetener for soft drinks if APM-sweetened beverages in certain parts of the country would, during the summer months, have to be treated as if they were perishable commodities?*/

[TO BE EXPANDED WITH AGE DISTRIBUTION DATA.]

---

*/ In the preamble to the APM regulation, FDA dismissed summarily the concern about the functionality of APM in soft drinks at temperatures above 30°C (86°F): "The agency believes, however, that storage at these times and temperatures can be avoided by attention to handling and distribution." (48 Fed. Reg. at 31377). This summary resolution of the functionality issued is inconsistent with the FDC Act for two reasons. First, it is based on the agency's "belief" and not on any objective evidence. The Act requires the agency to resolve material issues based on facts, not on beliefs. Moreover, the facts -- actual temperature conditions to which the beverages are exposed and actual beverage temperatures -- suggest that degradation and consequent loss of sweetness and overall liking (and hence functionality) may occur within even shorter periods than the agency appeared to find acceptable. Second, the purported resolution of the functionality issue by assuming that significant loss of sweetness "can be avoided by attention to handling and distribution" is an assumption unsupported by any evidence in the present record (none is cited by the agency). In all likelihood, the agency's "resolution" is entirely impracticable. To assume that fundamental changes in handling and distribution will occur to avoid an acknowledged functionality problem turns the FDC Act on its head.

Objection No. Four: G.D. Searle and Company Has Not Demonstrated To A Reasonable Certainty That The Use of Aspartame In Soft Drinks, Without Quantitative Limitation, Will Not Adversely Affect Human Health As A Result Of The Changes Such Use Is Likely To Cause In Brain Chemistry And Function Under Certain Reasonably Anticipated Conditions Of Use.

Summary of Basis for Objection

In its July 8 Federal Register notice, FDA acknowledged receiving a comment expressing concern about the effect on plasma and brain phenylalanine (PHE) and tyrosine (TYR) levels when aspartame is fed in combination with a carbohydrate. 48 Fed. Reg. at 31379. The comment included data demonstrating that in both rats and humans the feeding of a carbohydrate with aspartame significantly enhances aspartame's positive effect on the ratio of PHE and TYR to other large neutral amino acids (LNAA) in the blood. The data submitted with the comment also demonstrate that brain PHE and TYR levels in the rat are significantly increased by the aspartame/carbohydrate combination.

The concern of the commenter, Dr. Richard J. Wurtman, Professor of Neuroendocrine Regulation at the Massachusetts Institute of Technology, was that increased brain levels of PHE and TYR are likely to affect the synthesis of certain neurotransmitters -- substances vital to the regulation of brain function -- and that changes in the levels of neurotransmitters could in turn cause adverse physiological effects (by, for example, modifying the function of the autonomic nervous system) and/or behavioral effects.

FDA responded to Dr. Wurtman's comment by stating that it "... believes that the comment's conclusion regarding potential phenylalanine induced changes in neurotransmitter function appear to be unwarranted extrapolations ..." (48 Fed. Reg. at 31379; emphasis added) and by concluding that "...the data supplied with this comment do not provide support for its hypothesis that the ingestion of aspartame and carbohydrate will alter the brain levels of neurotransmitters and thereby produce behavioral modifications." 48 Fed. Reg. at 31380. FDA cited as support for its conclusion several studies submitted by Searle; FDA did not discuss, however, much of the data submitted by Dr. Wurtman (including those demonstrating significantly elevated brain levels of PHE and TYR), and it apparently overlooked the significance of aspartame's demonstrated blocking effect on glucose-induced elevation of brain serotonin levels.

In light of the allocation of the burden of proof and the nature of the safety standard in food additive proceedings (discussed above), FDA's handling of Dr. Wurtman's concerns was unusual. The tone of the July 8 notice suggested that the burden was on Dr. Wurtman to demonstrate that aspartame is harmful and that, absent affirmative demonstration of harm (which obviously is lacking at this point), aspartame must be approved. To the contrary, however, the burden is on Searle to prove to a reasonable certainty that no harm to human health will result from aspartame. Thus, the question for FDA in evaluating Dr. Wurtman's concern is whether, in the minds of competent scientists, the questions posed by Dr. Wurtman and his data are sufficiently significant from a safety standpoint that they should be more thoroughly addressed by Searle in order to provide the statutorily required "reasonable certainty" that no harm will result from aspartame's use.

We object to the approval of aspartame for unrestricted use in soft drinks (which could be as high as 550 mg/liter, or higher) on the ground that Searle has not made the required showing. This objection is supported by the following points, which are discussed further below and supported by the accompanying affidavits: (1) available evidence demonstrates that the consumption of aspartame/carbohydrate combinations by rats in amounts comparable to those likely to be encountered by humans under certain reasonably anticipated conditions of use elevates plasma ratios of PHE and TYR significantly and brain PHE and TYR levels by factors of 3.0 and 3.5, respectively; (2) available evidence from human studies demonstrates that consumption of aspartame/carbohydrate combinations in amounts likely to be encountered under certain reasonably anticipated conditions of use elevates human plasma levels of PHE significantly beyond the normal range; (3) there are sound scientific reasons to believe that human brain levels of PHE and TYR will respond to aspartame consumption in a manner similar to rats; (4) there are sound scientific reasons to believe that increased brain levels of PHE and TYR could affect the synthesis of neurotransmitters and in turn various physiological functions and/or behavior; for example, TYR is a known precursor of the catecholamine neurotransmitters, and tyrosine levels have been shown to affect several bodily functions controlled by the autonomic nervous system (including regulation of blood pressure); and (5) the demonstrated ability of aspartame to inhibit the glucose-induced release of serotonin has the potential to affect important serotonin- mediated behaviors, such as satiety, food choice, and sleep.

Despite the potential effects of aspartame/carbohydrate combinations, the present record is devoid of readily obtainable evidence that could resolve whether the effects are in fact likely to occur. As will be demonstrated, the data cited by FDA in its July 8 notice are not sufficient to resolve the issue. It would be possible, however, to perform within approximately six months studies in rats that would resolve conclusively whether levels of aspartame and carbohydrate corresponding to those likely to be consumed by humans would affect the synthesis of neurotransmitters and in turn cause detectible physiological and behavioral effects. It also would be possible to perform additional short-term studies in humans to determine whether aspartame/carbohydrate combinations have observable effects on physiological parameters (such as blood pressure) or behavior.

For these reasons, Searle has not met its burden of demonstrating to a reasonable certainty that the unlimited use of aspartame, especially in combination with carbohydrates, will not adversely affect human health. The questions posed by Dr. Wurtman are significant because of the seriousness of the potential effects (e.g., changes in blood pressure) and because of aspartame's anticipated widespread use--use that includes consumption by potentially vulnerable sub-groups, such as children, pregnant women, and hypertensives. Dr. Wurtman's concerns are shared by other distinguished scientists expert in this field (affidavits attached). It is Searle's legal burden to submit data sufficient to resolve the concerns.

Factual Information Supporting Objection Four

1. FDA has underestimated the amount of aspartame that can be consumed through its use in soft drinks because the agency has focused on adult users (assumed to average 60 kilograms in weight). FDA relied upon an intake value of 34 mg/kg/day in assessing the possible risks of aspartame, describing that level as the "... highest obtained from any estimate of potential consumption and exceed[ing] the 99th percentile consumption (25 mg/kg) for all age groups ..." 48 Fed. Reg. at 31377. For a 30 kg child, however, it would not be unusual for that level to be achieved or, in terms of the effect on plasma PHE levels, even exceeded. For example, if a 30 kg child consumed on a warm day after exercise approximately two-thirds of a two-liter bottle of soft drink sweetened solely with aspartame, that child would be consuming approximately 700 mg of aspartame, or approximately 23 mg/kg. This alone roughly

equals what FDA considered the 99th percentile consumption level. If during the day this child consumed other aspartame-sweetened products, the exposure level could quickly approximate FDA's so called "loading dose" of 34 mg/kg. 48 Fed. Reg. at 31377. In addition, however, data derived from rats and humans demonstrate that concurrent consumption of a modest amount of carbohydrate (approximately 3 grams per kg, or, for a 30 kg child, perhaps several cookies) approximately doubles the effect of the aspartame on the ratio of plasma PHE to other large neutral amino acids (LNAA) (Wurtman affidavit). Thus, in terms of effect on the PHE/LNAA ratio in the blood, the above-described concurrent consumption of aspartame and a carbohydrate is equivalent to an aspartame dose of as much as 50 to 60 mg/kg.

2. Aspartame has been tested in rats to determine the effect of aspartame and aspartame/carbohydrate combinations on the plasma ratios and brain levels of various amino acids (Wurtman affidavit). In rats fed 200 mg/kg aspartame, the plasma PHE/LNAA ratio increased to 0.185 from 0.110 in the controls, and the brain PHE level increased from 52 n-moles/g in the controls to 110 in the treated animals. When the same amount of aspartame was fed with 3 g/kg glucose, however, the plasma PHE/LNAA ratio increased sharply again to 0.240, while the brain PHE level increased to 143 n-moles/g. In addition, there was a 3.5-fold increase in brain TYR levels.

3. Aspartame and aspartame/carbohydrate combinations have

also been tested in humans by Searle and Dr. Wurtman (cite to Searle petition and Wurtman affidavit). An aspartame dose of 34 mg/kg significantly elevated the plasma PHE/LNAA ratio, an effect that is almost doubled by the addition of 30 g of carbohydrate (equivalent to 4 or 5 cookies).

4. It is not possible to measure *in vivo* human brain levels of amino acids resulting from consumption of aspartame or subsequent effects on neurotransmitter synthesis. There are sound theoretical reasons, however, for considering the rat to be an appropriate model for assessing possible human effects (Wurtman affidavit). Moreover, there is empirical evidence to support the use of the rat as a model for evaluating possible effects of aspartame on human brain chemistry (Wurtman affidavit).

5. There is scientific evidence suggesting that increases in brain PHE and TYR levels on the order seen in the rat studies can affect synthesis of neurotransmitters, which themselves can affect important physiological functions and potentially behavior. [Wurtman affidavit should catalogue this evidence.] Readily available tests could determine whether aspartame has such neurotransmitter effects in rats or affects the rat's physiological functions or behavior. [Wurtman affidavit should describe tests.]

6. Aspartame has been demonstrated to inhibit the carbohydrate-induced synthesis of the neurotransmitter serotonin (Wurtman affidavit). Serotonin blunts the sensation

of craving carbohydrates and thus is part of the body's feedback system that helps limit consumption of carbohydrate to appropriate levels. Its inhibition by aspartame could lead to the anomalous result of a diet product causing increased consumption of carbohydrates.

Mr. ROBERTS. I would just add if I may, Senator Metzenbaum, that having lived through the experience of cyclamate and saccharin in our industry, we were bound and determined that we would look at aspartame approval for use in soft drinks every which way from Sunday, and including the possible objections that might be raised by some people, before we were satisfied enough to use it in our products. We learned from history.

The CHAIRMAN. It should be noted that that was not a final document of your organization, and if you want to submit any evidence to that regard, we will be happy to include that in the record.

Mr. ROBERTS. I have no objection at all to including the document in the record, but I would also like to include an explanation putting it in perspective. I will submit that explanation for the record.

Senator METZENBAUM. You claim in the document that FDA should have required further testing on Dr. Wurtman's brain chemistry issue before approval. Is that fair to state? The document that wasn't filed, but the document that was prepared to be filed——

Mr. ROBERTS. You are quoting from that document, Senator, so obviously that is in there.

Senator METZENBAUM. And in that document, I should point out that you claim that Searle did not identify NutraSweet's decomposition products and that, as a result, quote, judgments about the safety of aspartame in soft drinks cannot be made confidently, end of quote.

I will not ask you to identify those decomposition products, but my line of inquiry is not to take issue with you but to indicate that at one point your organization did, indeed, have very serious concerns about the safety and the value of using aspartame in soft drinks.

Mr. ROBERTS. Of course, that is very true. In today's world, we have equal concerns about any new ingredient.

Senator METZENBAUM. About what?

Mr. ROBERTS. About any new ingredient that we might use in soft drinks.

Senator METZENBAUM. Now, would your organization have any difficulty if it came to pass that either the FDA or Congress required the disclosure of the amount of aspartame on the bottles or cans? Would that bother you at all?

Mr. **Roberts**. As I have indicated, Senator—and I would be glad to give you this copy that I brought along with me—such information about the content of aspartame in soft drinks is already made available by our organization.

Senator **Metzenbaum**. But that is in a piece of paper that you—how do you get that piece of paper?

Mr. **Roberts**. It is available free from our organization, and we try to make its existence known to a variety of groups. On each of these issues, there are thousands and thousands that are mailed out to a prescribed mailing list, and we try to identify in public sources that such information is in fact readily available from our organization.

Senator **Metzenbaum**. So that it really would not be any major impediment to sales; it might be one more line you would have to find on the can or the bottle, but other than that, it wouldn't be of any major significance to you?

Mr. **Roberts**. I would make a distinction between providing the information and prescribing it in some particular format on a product label, Senator.

Senator **Metzenbaum**. Well, maybe we could figure out some one little thing to drop off here.

Mr. **Roberts**. OK. Maybe we can negotiate and drop a few lines and add something that would be better.

Senator **Metzenbaum**. All right, because, you see, here is diet Pepsi, and they have a great big ad, "Now, no saccharin, 100 percent NutraSweet," which is fine, and I have no quarrel with them in that respect. Then they have "NutraSweet brand sweetener" down below, and they make quite a deal of it, and they say, "One calorie."

So, I would guess that, somewhere on this can, they could put in a little item such as is done by Tempo. Who owns Tempo? Is that Pepsi or Coca-Cola?

Mr. **Roberts**. I am not familiar with that Israeli brand.

Senator **Metzenbaum**. It looks like the logo of—I don't know.

Mr. **Roberts**. I don't know the origin. That could be an Israeli brand. I am not sure.

Senator **Metzenbaum**. And they do carry it on there. In fact, they even have the warning. I might say that at this moment, I am not at all certain whether we should go that far with respect to the warning as to how much you can ingest, because I am not certain that we have enough information. I think there may be real value in indicating the amount and, perhaps at a later date, going back and saying what the legal limit would be.

I notice that Dr. Stegink and Dr. Wurtman had a little different points of view. But you wouldn't see this as being intolerable?

Mr. **Roberts**. Giving that information, no, although I would also add the point that I certainly have no concern about the levels of aspartame that are, in fact, used in soft drinks.

Senator **Metzenbaum**. I thank you. I have no further questions, Mr. Chairman.

The **Chairman**. Well, thank you, then, Senator Metzenbaum.

I would like to thank all the witnesses for their informative testimony here today. We have had some very interesting testimony, and I ask that the answers to be furnished in writing from questions from members of the committee be turned in by Friday, April 10.

Without objection, we will also hold the hearing record open until then for the receipt of additional written statements. I have in hand statements from the Calorie Control Council, the National Food Processors Association, the American Council on Science and Health, Dr. William Havendar, and Dr. Abraham I. Bakal. These will be included in the record, also.

In addition, Senator Dodd has a question here for Dr. Young and two questions for Dr. Wurtman, so without objection, we will have staff get those questions to both of them and have them answered for the record.

[Statements subsequently submitted for the record follow:]

STATEMENT OF ROBERT H. KELLEN
PRESIDENT, CALORIE CONTROL COUNCIL
SUBMITTED APRIL 2, 1985 FOR THE
SENATE LABOR AND HUMAN RESOURCES COMMITTEE HEARING ON SWEETENERS

The Calorie Control Council and its members appreciate the opportunity to provide this statement to the Committee. We ask that it be included in the official hearing record.

The Calorie Control Council is an international association representing 60 manufacturers and suppliers of dietary foods and beverages. Our membership includes the manufacturers of more than 12 different dietary sweeteners, including acesulfame K, aspartame, cyclamate and saccharin, as well as the food and beverage companies that utilize these sweeteners in hundreds of different products.

Since its inception in 1966, the Council's philosophy has been to support the development and approval of a wide variety of safe low-calorie sweeteners for use in the food supply. A variety of sweeteners provides a valuable opportunity for the dietary food and beverage industry to meet the rising consumer demand for new and better-tasting reduced-calorie products. At the same time, this variety reduces consumption of any single sweetener to levels well below those already considered safe.

Careful attention to scientific research has been a cornerstone of the Council since its founding. Based on a thorough review of the scientific evidence, the Council supports the continued availability of saccharin and emphasizes the importance of saccharin as the foundation of dietary foods and beverages. The Council also welcomes the availability of aspartame and urges the approval of acesulfame K and reapproval of cyclamate. These sweeteners have extensive scientific evidence supporting their safety. Because no one sweetener is ideally suited for all applications, the Council believes the public will be served best by a wide variety of safe sweeteners.

In light of this philosophy, the Council supports the passage of S.484 to extend the saccharin ban moratorium. Since it was first passed in 1977, the Congressional moratorium preventing a Food and Drug Administration (FDA) ban of saccharin has been extended three times. The reasons for the previous extensions -- overwhelming scientific evidence supporting saccharin's safety, support from scientific, medical and regulatory authorities worldwide, and the public's continued desire for saccharin -- remain important today. Additionally, the moratorium extensions are allowing time for ongoing consideration of changes in food safety laws and for the completion of further saccharin research.

Saccharin has been used to safely sweeten foods and beverages for nearly a century and is one of the most studied substances in our food supply. The extensive research supporting saccharin's safety includes 14 single-generation animal studies and some 20 human-use studies, including studies of long-term users such as diabetics, in which saccharin was not found to induce cancer. The human research includes seven studies completed during the past five years which further support saccharin's safety for human consumption.

In 1980, the National Cancer Institute (NCI) published the findings of one of the largest-ever human bladder cancer studies. In its report NCI noted that "in the total study group (which included 9,000 individuals) there was no evidence of increased risk with long-term use of AS (artificial sweeteners) in any form or with use that began decades ago." An independent review of the study, conducted by Epidemiology Resources, Inc., reconfirmed the overall favorable finding of the NCI study and further concluded that "the data provided little evidence that non-nutritive sweeteners increase risk for bladder cancer among subgroups of users."

A July 1984 review of epidemiologic studies of artificial sweeteners by Robert W. Morgan, M.D., senior physician epidemiologist, Environmental Health Associates, noted, "Few chemicals have been studied epidemiologically to the same extent as artifical sweeteners (saccharin and cyclamate) have been. The remarkable approximation to unity of the summary relative risk from all studies is impressive, and one wonders how many common foodstuffs would test to be that safe."

The saccharin controversy has centered primarily around high-dose rat studies in which the most sensitive strain of rat was fed the human equivalent of the saccharin in hundreds of cans of diet soft drink a day, for a lifetime. Even then, the tests produced bladder tumors only in some of the male rats at the highest doses.

The Calorie Control Council sponsored a recently completed high-dose rat study, conducted at the International Research and Development Corporation (IRDC), to examine the relationship between high doses of saccharin, the resulting abnormal physiology and tumors in the male rat. In May 1983, an international panel of distinguished scientists met at Duke University Medical Center to review saccharin research, including the IRDC study. Among the panel's conclusions was the following: "The results of the IRDC study, by better defining the dose-response relationship for bladder tumor risk in the rat, support the conclusion that the present level of exposure of humans to saccharin through its use as a food additive is unlikely to present a cancer risk."

Although no study report has been published, an analysis of the preliminary data of rat and mouse saccharin promotion studies recently conducted at the National Center for Toxicological Research provide further evidence of saccharin's safety for human consumption. The mouse study results did not show that saccharin promotes tumors, while the results of the rat study were inconclusive. The findings of both studies provide further indication that previous experiments with rats represent an effect unique to that species. The scientific panel which reviewed the IRDC study also noted, "The appearance of tumors in rats seems to be a species- and organ-specific phenomenon for which there is at present no explanation." In addition to the extensive favorable human studies, saccharin has not been shown to cause tumors in studies of mice, hamsters and monkeys.

The Duke scientific review panel recommended further studies in the ongoing research program aimed at identifying the mechanism of tumor occurrence in rats. One of these studies will investigate sodium as a causative factor. (Recent evidence indicates that it may be the sodium in the experiments that caused tumors in rats at very high levels.)

Saccharin is approved in more than 80 countries around the world and has been reviewed and determined safe by the Joint Expert Committee on Food Additives of the World Health Organization (JECFA) and by the Scientific Committee for Food of the Commission of the European Economic Communities.

In 1984, JECFA reaffirmed its previous conclusions approving saccharin for human use. JECFA concluded that the epidemiological data do not show any evidence that saccharin is a human bladder carcinogen and determined a no-effect level in the rat. Also, Great Britain recently confirmed the continued marketing of saccharin. Following the favorable recommendation of the British Committee on

Toxicity, which reviewed the scientific evidence on saccharin, the United Kingdom's Food Additives and Contaminants Committee proposed regulations allowing for the continued use of saccharin in foods. These regulations went into effect in September 1983.

Many important scientific and health organizations interested in low-calorie sweeteners have reviewed the extensive scientific research on saccharin and have issued statements supporting its availability. These groups include the American Diabetes Association, the American Society of Bariatric Physicians, the American Medical Association, the American Society of Internal Medicine, the Juvenile Diabetes Foundation and the American Council on Science and Health.

Saccharin should remain available in the U.S. for the more than 68 million Americans who regularly use low-calorie foods and beverages to help them control caloric and carbohydrate intake. Research conducted by the Council shows that people believe products containing low-calorie sweeteners help them stay in better overall health and maintain an attractive physical appearance. Research also shows that health professionals concur that saccharin is beneficial to many people such as diabetics and the obese, and helps inhibit dental caries.

The dietary food and beverage market has experienced a dramatic change as a result of the 1981 approval of aspartame in various foods and dry beverages, and its expanded approval in 1983 for use in carbonated beverages. The rapid rise in aspartame's popularity can be attributed to the many benefits it provides calorie-conscious consumers. Aspartame-sweetened products offer promising opportunities for controlling weight, improving dental health and expanding low-calorie food and beverage choices.

In approving aspartame, then-FDA Commissioner Dr. Arthur Hayes found that evidence indicated aspartame to be safe at expected levels of consumption and at the highest conceivable levels of consumption. Commissioner Hayes noted, "Few compounds have withstood such detailed testing and repeated, close scrutiny, and the process through which aspartame has gone should provide the public with additional confidence of its safety." It is important to note that aspartame was approved by FDA after more than a decade of regulatory examination and on the basis of more than 100 scientific studies.

In 1984, both FDA and the Centers for Disease Control reaffirmed the safety of aspartame. In addition, JECFA, the Scientific Committee for Food of the Commission of the European Economic Communities and regulatory agencies in 40 countries have reviewed and approved aspartame. This sweetener is one of the most thoroughly tested and scrutinized substances in the food supply.

Petitions have been submitted to FDA for approval of aspartame's use in refrigerated/frozen beverages, non-carbonated beverages, ready-to-serve gelatin desserts, breath mints, frozen fruit juice-containing confections and for use in bulk package form. The Council urges FDA to approve aspartame for these uses.

The Council also encourages the reapproval of cyclamate, a popular low-calorie sweetener not available in the U.S. since 1970. A cyclamate/saccharin blend was widely used in diet soft drinks in the 1960s. Currently, cyclamate is approved in more than 40 countries. In 1982, a petition to FDA for the return of cyclamate to the U.S. market was submitted jointly by the Calorie Control Council and Abbott Laboratories. The petition includes extensive new data supporting cyclamate's safety. In 1984, FDA's Cancer Assessment Committee (CAC) reviewed the scientific evidence and reached the following conclusion: "[T]he collective weight of the many experiments...indicates that cyclamate is not carcinogenic." At FDA's request, the National Academy of Sciences (NAS) is undertaking a review of the possible carcinogenicity of cyclamate and will consider the CAC's report. The NAS review is expected to be completed by May 1985.

We believe FDA has a historic opportunity to advance the cause of objective, scientific decisionmaking and to correct the misinformation and unscientific analysis which removed cyclamate from use in the U.S. Cyclamate will not replace saccharin or aspartame in products where either is the sole sweetener, but is extremely useful in combination with other sweeteners.

FDA also is reviewing a petition, filed by the American Hoechst Corporation, for approval of another low-calorie sweetener, acesulfame K. Currently, acesulfame K is approved for various uses in the United Kingdom, Switzerland and Germany. The technological characteristics of acesulfame K make it viable for use in almost all areas where sweeteners are presently being used. Testing has shown good performance in soft drinks, juices, fruit preparations, milk products, candies and chewing gums, as well as in tabletop application. It also appears to be suited for use in toothpaste, mouthwashes and pharmaceuticals. Based on a review of the acesulfame K study data, the Council is encouraged about its prospects for use by the dietary food and beverage industry and supports its approval.

Many other sweeteners are on the horizon, but their availability in the U.S. is most likely a long-term proposition. It is important to remember that the perfect, all-purpose low-calorie sweetener does not exist. For this reason, the availability of a variety of safe low-calorie sweeteners is important -- to industry and consumers -- so that the growing consumer demand for more and better-tasting reduced- calorie products can be met. Additionally, the availability of a variety of sweeteners reduces consumption of any single sweetener to levels well below those already considered safe. The British government supports this multiple sweetener approach and has made it a reality by approving a variety of sweeteners including saccharin, aspartame, acesulfame K and thaumatin.

The availability of both saccharin and aspartame in the U.S. has enabled many manufacturers to use the most appropriate sweetener for a given product and to use the two sweeteners in combination. Using sweetener blends has helped the strength of one sweetener compensate for the limitations of another. The combination approach provides increased product stability, improved taste, reduced consumption of individual sweeteners, lower manufacturing costs and a greater variety of products for the consumer.

Although the total amount of saccharin used today is less than in the past, it remains a useful ingredient in diet soft drinks -- particularly in fountain soft drinks where aspartame's stability limitation is magnified. Saccharin also is a necessary ingredient in many food, cosmetic and pharmaceutical products in which saccharin is the only approved low-calorie sweetener, or aspartame alone is not functional. For example, aspartame loses its sweetness when heated for long periods, making saccharin the preferred low-calorie sweetener in cooking and baking and in foods requiring heat processing.

The availability of a wide variety of safe low-calorie sweeteners, including the continued availability of saccharin and aspartame, is important to the millions of Americans who use products containing them. It is important to note that no sweetener is as versatile as saccharin. Other sweeteners complement saccharin but cannot replace it. Those using saccharin today use less than before, want to keep using it and have no substitute for many of its uses. It is for these people that Congress should once again extend the saccharin ban moratorium. If saccharin were removed from the food supply, it would mean the loss of a substantial benefit to many for the sake of a very theoretical risk. With the continued availability of saccharin, expanded approvals of aspartame, and approvals of other safe low-calorie sweeteners like cyclamate and acesulfame K, a greater variety of good-tasting products will be available to help consumers control their diets while they enjoy eating.

nfpa
National Food Processors Association
1401 New York Ave., N.W.
Washington, D.C. 20005
202/639-5900

**Statement
of the
National Food Processors Association
on S. 484
Saccharin Study and Labeling Act
For the Record of the
Committee on Labor and Human Resources
United States Senate
April 2, 1985**

The National Food Processors Association (NFPA) is a scientifically and technically based trade association that represents about 450 food processing companies that pack processed-prepared fruits, vegetables, meats, fish, and specialty products including canned, aseptic, frozen, dehydrated, pickled and other preserved food items. We are pleased to have this opportunity to comment for the record regarding the Saccharin Study and Labeling Act, S. 484.

NFPA and its members support S. 484 which would extend until May 1, 1988, the moratorium on Food and Drug Administration regulatory efforts to remove saccharin from the market. Although there is an alternative low calorie sweetener for some food uses, for products that are heat processed saccharin remains the sole low calorie sweetener approved by FDA. Saccharin will withstand the heat processing necessary for the production of a variety of products processed by NFPA members such as canned fruits and fruit juices, syrups, jams and jellies, and salad dressings and will retain its sweetness value over the life of the products.

Aspartame has been approved as an alternative low calorie sweetener for saccharin in a limited number of food uses. But

FDA regulations (21 CFR 172.805) restrict aspartame use as a sweetener to the following food groups:

(1) dry, free flowing sugar substitute for table use (not to include use in cooking) in package units not to exceed the sweetening equivalent of 2 teaspoonsful of sugar;
(2) sugar substitute tablets for sweetening hot beverages, including coffee and tea;
(3) cold breakfast cereal;
(4) chewing gum;
(5) dry bases for:
    (i) beverages
    (ii) instant coffee and tea
    (iii) gelatins, puddings, and fillings
    (iv) dairy products analog toppings;
(6) carbonated beverages and carbonated beverage syrup bases;
(7) chewable multivitamin food supplements; and
(8) as a flavor enhancer in chewing gum

FDA has under review several food additive petitions requesting that further food categories be added to this list. However, the labile (unstable) nature of aspartame when heated precludes its use in a number of food categories. When subjected to thermal processing temperatures, such as those encountered in producing commercially sterile canned fruits or fruit juices, aspartame will break down into its components L-phenylalanine and L-aspartic acid and lose its sweetness. Therefore, for many NFPA members with low calorie products, there is presently no viable substitute for saccharin.

NFPA members produce a wide variety of low calorie products containing saccharin. As an industry that processes food products for the public's consumption, our members want to use only the safest of food additives. The popularity of these products attests to the value of saccharin in enhancing their attractiveness in the safest possible way without increasing their natural caloric content.

To ensure that consumers know whether a product contains saccharin or not, the Saccharin Labeling Act of 1977 (P.L. 95-203 enacted November 23, 1977), which amended the Federal Food Drug and Cosmetic Act, (Sec. 403(o)) provides explicit labeling requirements for all products which contain saccharin. These label statements adequately inform the consumer that the product contains saccharin and allow the consumer to exercise a choice in purchasing the product.

In the absence of suitable substitutes for saccharin in many food uses, a substantial number of low calorie products would either cease production or be forced to employ alternate sweeteners, such as corn syrup, which contain relatively more calories thereby reducing their utility to dieting consumers. Artificial sweeteners are a vital need in the diet of diabetics and dieting consumers under the care of a physician. Also, the introduction of aspartame as a substitute for saccharin in several food categories has led to a reduction in the dietary intake of saccharin from all sources.

In light of these facts, NFPA asks that the Congress approve an extension of the Saccharin Labeling Act to provide for the continued availability of a wider variety of low calorie food products for the diet conscious consumer.

American Council on Science and Health

Elizabeth M. Whelan, Sc.D., M.P.H.
Executive Director

Richard A. Greenberg, Ph.D.
Associate Director

Lynne P. Middelveen, M.S.
Assistant Director

1985 MAR 11 AM 9 26

March 8, 1985

RECEIVED MAR 18 1985

The Honorable Orrin G. Hatch
Senate Office Building
Washington, DC 20510

Re: S. 484, "Saccharin Study and Labeling Act"

Dear Senator Hatch:

I am the executive director of the American Council on Science and Health (ACSH), an independent, national, nonprofit scientific consumer education association. Our organization recently reviewed the scientific evidence on the health effects of saccharin (see the enclosed report), and on the basis of that review, we see no reason why saccharin should not continue to be available to the public.

Since the Saccharin Study and Labeling Act was passed in 1977, substantial additional scientific research has been completed which supports the conclusion that saccharin, at customary levels of use, does not pose a threat to human health.

In particular, I would like to call your attention to the extensive study of saccharin and bladder cancer in rats conducted by the International Research and Development Corporation (IRDC). The dose-response data obtained from this study indicates that the hypothetical increased risk of bladder cancer caused by exposure to saccharin at ordinary human consumption levels is negligible. Mathematical models indicate that exposure to saccharin at a level of 0.01 percent of the diet (about 2.3 12-ounce cans of saccharin-sweetened diet beverage per day) over a lifetime would increase the chance of developing bladder cancer by considerably less than one in a million.

The IRDC study also showed that a number of physiological changes occur in rats fed high doses of saccharin which do not occur in human saccharin consumers. Several of these changes, including some which specifically affect the urinary system, occur only in rats fed the very high doses associated with tumors, and do not occur in rats fed lower doses. These changes might be responsible for the production of bladder tumors; further research is needed to clarify this. But there is certainly a strong possibility that there may be no cancer risk at all associated with the consumption of saccharin at lower doses.

I would also like to call your attention to the extremely large epidemiological study of artificial sweeteners and bladder cancer conducted by the National Cancer Institute (NCI). This study, one of the largest of its kind ever conducted on any disease, found no association between artificial sweetener use and bladder cancer in the overall groups of men, women, or both sexes combined. There has been considerable discussion about hints of possible slight effects in tiny population subgroups in this study. However, these effects have never been confirmed by any other study and are most likely due to chance. We do not believe

Please Reply to:
☒ 1995 Broadway 18th Floor New York, NY 10023 Telephone: (212) 362-7044
☐ 47 Maple Street Summit, NJ 07901 Telephone: (201) 277-0024
☐ 1050 17th Street, N.W. Suite 900 Washington, D.C. 20036 Telephone: (202) 659-8978

that they have any practical relevance.

The total body of epidemiological evidence on saccharin, including the NCI study, is very reassuring. The investigations have been extensive. Indeed, few other substances have been examined so thoroughly. Yet these studies have not provided evidence that saccharin consumption is associated with an increased risk of bladder cancer in human beings.

The totality of evidence gathered from animal and human studies of saccharin has been unable to confirm that there is any risk to the human population from the use of saccharin in normal dietary amounts. Thus, we believe that saccharin should be regarded as a safe food additive.

We believe that consumers benefit if several safe low-calorie sweetening agents are available. A competitive situation can lead to the development of higher-quality and lower-cost products and increase the variety of dietary foods and beverages available to the public. There is no one ideal, all-purpose low-calorie sweetener, so if several are available, each can be used in the applications for which it is best suited, and consumer exposure to a single low-calorie sweetener will be lessened. Therefore, we believe that consumers will benefit if saccharin remains on the market.

Sincerely,

Elizabeth M. Whelan
Executive Director

Encl: Low-Calorie Sweeteners report

EMW:kam

WILLIAM R. HAVENDER, Ph.D.
One Eagle Hill
Berkeley, CA 94707
Tel: (415) 524-2791

1985 MAR -4 PM 3: 2

March 1, 1985

RECEIVED MAR 7 1985

Senator Orrin G. Hatch
Senate Office Building
Washington, D.C. 20510

Dear Senator Hatch:

This letter is in support of S. 484, the bill to extend the Saccharin Study and Labelling Act for another three years. The reasons why I, a scientist competent in this area, strongly support S. 484 are given below.

There is now no doubt that saccharin can cause cancer in rats, because four replicate experiments have shown that a low incidence of non-lethal bladder tumors can indeed be induced in male rats when exposure to maximally tolerated doses commences with their dams and is continued over a lifetime. Nevertheless, consideration of all of the evidence in hand shows that the cancer risk to humans from the normal consumption of saccharin is certainly negligible, and in all likelihood nonexistent.

Conservative risk estimates made in 1977 by the Office of Technology Assessment indicate that the number of cancer cases to be expected in a population the size of the United States from the lifetime consumption of one diet soda per person per day would be no more than a few thousand per year (as an upper bound). Even this estimate has always been fictitious, since it made no allowance for actual consumption patterns (which are much, much smaller than those assumed, and are now getting even smaller because of competition from Nutra-Sweet), and entirely ignored the fact that the so-called "two-generation" animal test protocol (in which exposure during conception, gestation, and pre-weaning stages is effected by means of the dosing of the dams, and which early exposure is necessary in order for a statistically significant incidence of tumors reliably to be seen) has never been validated with regard to human risk prediction. Virtually the entire sum of information we presently have concerning the reliability of cancer risk predictions made to humans from animal tests is derived from experimental designs where exposure to the test chemical commences only after weaning. In particular, the common opinion that properly designed animal tests rarely miss human carcinogens comes entirely from tests of this sort. In the case of saccharin, all tests in animals where exposure commences only after weaning have been, with one marginal and disputed exception, statistically negative, and therefore, by the standard of interpretation normally applied to animal tests, saccharin should be considered to pose no cancer risk to humans at all. Which test design -- with or without pre-weaning exposure -- is the more accurate predictor of human risk in the cases where, as here, these test designs give opposite results is completely unknown. But the fact that "false negative" results are so rare (only arsenic among the known human carcinogenic chemicals has not so far been shown to cause cancer in test animals) argues that the protocols without pre-weaning exposure are substantially better validated, and therefore their negative verdict should prevail.

Be this as it may, there is now available a dose-response study of high technical quality on saccharin which decisively shows that the cancer response is extremely non-linear with respect to dose. In fact, the data are consistent with a no-effect threshold at doses just slightly below the maximally tolerated dose and still far higher than those of normal human consumption. (Those skeptics who opined that saccharin-induced animal cancer was predominantly a high-dose phenomenon have, in fact, been vindicated!) And even if one chooses to be "conservative" by fitting a statistical model to the data that preserves the notion that even one molecule of a carcinogen poses some risk, however small, and projecting this model down to the dose levels typical of human consumption, the predicted risk is some 10,000 times lower than the OTA estimate cited above (which had been based on the assumption of strict linearity of the dose response). Reducing this earlier upper bound prediction of a "few thousand per year" by a factor of 10,000 wipes it out entirely.

It is therefore justified to conclude that saccharin poses a risk of cancer to humans that lies somewhere in the range from negligible to non-existent. I am enclosing a copy of a recent article by Dr. Elisabeth Whelan and myself that develops these arguments in depth, and also a recent brochure I wrote for the American Council on Science and Health (of which Dr. Whelan is the Executive Director) dealing with animal cancer tests and the interpretations that may properly be made from them.

Sincerely,

William R. Havender

William R. Havender

ABIC INTERNATIONAL CONSULTANTS, INC.
P.O. BOX 368
346 CHANGEBRIDGE ROAD
PINE BROOK, NEW JERSEY 07058
201-227-7060
TELEX - 642-024

85 MAR -4 [illegible]

February 26, 1985

RECEIVED MAR 7 1985

Senator Orrin G. Hatch
Chairman
Committee On Labor and Human Resources
Senate Office Building
Room 135
Washington, D.C. 20510

Honorable Chairman:

I am writing to you to express my support for Senate Bill S484 you recently introduced, together with Senators Kennedy, D'Amato, Hawkins, Stafford, Quayle, Pell and Eagleton.

I am a scientist and have been involved with sweeteners for a long time, thus I closely follow saccharin and cyclamate issues. I believe that most scientists agree that these compounds are safe food additives on the basis of the scientific evidence.

Saccharin has been subjected to more than 25 epidemiological studies, including a two generation study in Denmark. It has been shown conclusively that saccharin ingestion is not linked with any measurable risk for increased bladder tumors in man. Against this overwhelming human evidence, some laboratory tests show that under certain conditions (lifetime ingestion of very high concentrations of sodium saccharin) male rats of only one species develop bladder tumors. Independent analysis of these data leads to only one conclusion, that saccharin is safe for human consumption.

Indeed this is the conclusion reached by regulatory agencies of many countries, and most recently by the Joint Expert Committee of the World Health Organization. This, I believe, correctly reflects the view of most scientists who have studied the saccharin issue. Dr. Bernard W. Wagner, Chief, Department of Pathology, Overlook Hospital, who is thoroughly familiar with saccharin research expressed, I believe, the opinion of many of his colleagues when he stated in a recent address to the Toxicological Forum in Aspen, Colorado, "For me, saccharin is not a human carcinogen. In fact, I was delighted to see that it was available the last few days at coffee break".

I believe that saccharin should remain available even if new sweeteners are approved. Saccharin is an important part of the diet of many consumers. These consumers, I believe, should not be deprived of their choice to use a product which has withstood the human test for so many years.

As a scientist and a consumer of saccharin, I wish to thank you and the members of your committee for your support of saccharin.

Very truly yours,

AI Bakal

Abraham I. Bakal, Ph.D.
President

AIB:wnk

DUKE UNIVERSITY MEDICAL CENTER

Occupational Health Service

1985 MAR 11 AM 10:46

RECEIVED MAR 18 1985

March 6, 1985

The Honorable Orrin G. Hatch
Senate Office Building
Washington, D.C. 20510

Re: S. 484

Dear Senator Hatch:

I was pleased to learn that you recently introduced S. 484 to extend the Saccharin Study and Labeling Act for 3 years.

I am in constant touch with new developments in the toxicology of saccharin and am also familiar with epidemiological studies carried out on consumers of sweetening agents. It so happens that I recently lectured on saccharin in the course I teach at the University of North Carolina, Chapel Hill.

In my opinion the use of saccharin, in both foods and beverages, is acceptable and does not constitute a risk to human health. I fully concur that the Saccharin Study and Labeling Act should be extended.

Sincerely yours,

Leon Golberg

Leon Golberg, M.B., D. Sc., D. Phil.
Professor of Community/Occupational Medicine

Division of Community and Occupational Medicine • Box 2914
Durham, North Carolina 27710 • Telephone (919) 684-6677

AMERICAN SOCIETY OF
BARIATRIC PHYSICIANS
A NON-PROFIT CORPORATION
7430 E. CALEY AVE., SUITE 210 • ENGLEWOOD, COLORADO 80111 • (303) 779-4833

1985 MAR 27 AM 9 41

RECEIVED APR 12 1985
DU

OFFICERS
PRESIDENT
Fred M. Furr, M.D.
9217 Park West Blvd.
Bldg. E, Ste. 1
Knoxville, TN 37923
615-693-1302
PRESIDENT-ELECT
Robert E. T. Stark, M.D.
444 Osborn, Ste. 102
Phoenix, AZ 85013
602-248-7002
VICE-PRESIDENT
Peter D. Vash, M.D.
2080 Century Park E., #1700
Los Angeles, CA 90067
213-553-0804
SECRETARY-TREASURER
Raymond E. Dietz, D.O., F.A.S.B.P.
2039 N. 2nd Street
Harrisburg, PA 17102
717-233-4307
PARLIAMENTARIAN
Michael Summer, M.D.
13301 N. Meridian, Bldg. [illegible]
Oklahoma City, OK 73120
405-755-[illegible]
TRUSTEES
CHAIRMAN
Robert M. Johnson, M.D., F.A.S.B.P.
7409 [illegible] Dr.
Charleston, SC 29416
803-797-7033
Victoria E. Blank, M.D.
480 Post Road
Fairfield, CT 06430
203-255-1566
Robert E. McLain, D.O.
1154 Sylvania Avenue
Toledo, OH 43612
419-478-2444
G. James Berry, M.D.
6825 E. Hampden
Denver, CO 80224
303-757-4900
Leon Tchaoudjian, Jr., M.D.
1614 W. Central Road, [illegible]
Arlington Heights, IL [illegible]
[illegible]

March 21, 1985

The Honorable Senator Orrin Hatch
United States Senate
Russell Office Building
Washington, DC 20510

Dear Senator Hatch:

It is our understanding your Committee on Labor and Human Resources is reviewing the current moratorium preventing the proposed ban of saccharin. Senate Bill 484, and House Bill 791 would extend the saccharin ban moratorium for three more years. Our organization, the American Society of Bariatric Physicians strongly supports the continuance of the moratorium.

In previous years, when this matter has been considered, our organization has made official position statements. These statements are enclosed for your review and consideration. It is still the unanimous opinion of The Board of Trustees of our organization that the moratorium should continue. We would appreciate our position being reviewed by your Committee.

Thank you for your cooperation and consideration.

[redacted]

Executive Director

JFM/kkl

Enclosure

EXECUTIVE DIRECTOR
James F. Merker, CAE
7430 E. Caley Ave., Ste. 210
Englewood, CO 80111
303-779-4833
DIR. OF CONTINUING MEDICAL EDUCATION
Peter G. Lindner, M.D., F.A.S.B.P.
The Lindner Clinic
[illegible] Garfield Avenue
South Gate, CA [illegible]
213-[illegible]
DIR. OF PROFESSIONAL AFFAIRS
W. L. Asher, M.D., F.A.S.B.P.
[illegible] S. Broadway
Englewood, CO 80110
303-761-[illegible]

The Cosmetic, Toiletry and Fragrance Association, Inc.
1110 Vermont Avenue, N.W. Washington, D.C. 20005 (202)331-1770 Telex 89-2673

E. Edward Kavanaugh
President

March 28, 1985

RECEIVED APR [illegible] 1985

The Honorable Orrin G. Hatch
Chairman
Committee on Labor and Human Resources
Dirksen Senate Office Building
Room SD-428
Washington, D.C. 20510

Dear Senator Hatch:

On behalf of the Cosmetic, Toiletry and Fragrance Association, I would like to endorse S.484, which would extend the current moratorium on any ban of saccharin until May 1, 1988.

CTFA is the national trade association representing the cosmetic, toiletry, and fragrance industry. We have an active membership of more than 250 companies that manufacture or distribute approximately 90% of the finished personal care products marketed in the United States. In addition, CTFA includes more than 210 associate member companies from related industries, such as manufacturers of cosmetic raw materials and packaging materials.

Several of the products manufactured or distributed by our members contain saccharin. These products include dentifrices, mouthwashes, lipsticks and glosses, and douches. Saccharin plays an important part in the acceptability and effectiveness of these products. For example, the regular use of dentifrices and mouthwashes plays a major role in promoting good oral health. Adherence to a proper oral hygiene regimen depends highly on the acceptability of the taste of the products used. This is particularly true in the case of young children. In many instances, saccharin provides the pleasant taste essential for good oral hygiene.

No other sweeteners with all the advantages of saccharin is currently available for use in personal hygiene products. For this reason, we urge the passage of S.484. Your leadership on this issue is appreciated.

Sincerely yours,

Ed Kavanaugh

E. Edward Kavanaugh

THE PROPRIETARY ASSOCIATION
Suite 1200/1150 Connecticut Avenue, N.W./Washington, D.C. 20036
Phone (202) 429-9260/Telex 75 9293 (PA WSH)

1985 APR -5 PM 2:40

April 3, 1985

RECEIVED APR 12 1985

The Honorable Orrin G. Hatch
Chairman, Committee on Labor and
  Human Resources
United States Senate
428 Dirksen Senate Office Building
Washington, D.C. 20510

Dear Mr. Chairman:

I am writing in support of your bill — ~~S. 484~~ which would amend the "Saccharine Study and Labeling Act" to extend the current moratorium prohibiting the Food and Drug Administration (FDA) from banning saccharin for another three years to May 1, 1988. The Proprietary Association (PA) is the century-old national trade association representing the manufacturers of nonprescription or over-the-counter medicines (OTCs), such as aspirin, cold tablets, cough syrups, and many others. Some of these products are among the most commonly used consumer products in the United States such as Bayer® Aspirin, Vicks Formula 44®, Anacin®, Bufferin®, Contac®, Tums®, and Tylenol®. PA members, large and small, account for about 95 percent of the sales of OTC medicines in the United States.

OTC drugs are an integral part of the health care system of the United States. OTC medicines provide safe and effective treatment for a multitude of ailments, enabling the public to forego time-consuming and expensive doctor visits and the attendant discomfort of delayed treatment. They are inexpensive and conveniently available in many thousands of retail outlets — including food stores, pharmacies, and discount and department stores — everywhere. Self-medication today constitutes an early and fundamental level of health care; without self-medication, physicians would be overwhelmed by patients seeking relief for symptoms and ailments that can be treated by self-care. Thus, use of OTC products for the treatment of conditions capable of lay diagnosis provide an economical and convenient alternative to understandably more costly physician visits.

The Proprietary Association supports passage of S. 484 and its companion House measure H.R. 791. Because a number of our member companies manufacture and make available medicines which contain saccharin and since there are very few, if any, suitable alternatives, favorable consideration of this legislation is in the public interest. Without saccharin many OTC drugs would no longer be palatable to the consumer. It is used in a wide variety of OTC medicines for this purpose. In fact, the PA recently has determined that its member companies produce at least 202 over-the-counter medicines which contain saccharin. These products include antacids, analgesics, sore throat remedies and oral antiseptics, nasal decongestants and expectorants, antidiarrheals and stomach remedies, toothpaste, mouthwashes and rinses, cough/cold remedies, laxatives, antiflatulents, oral topical infant-children liquids, vitamins, nutritional and dietary supplements, cold sore lotions, bronchodilators, anticaries, and flouride tablets.

The aggregate retail sales of OTC products containing saccharin is in exceess of $1.2 billion.

Continued use of saccharin as a sweetener in the over-the-counter medicines industry will enable manufacturers to continue to provide many safe and effective products at reasonable cost to the consumer. In many cases, there are no suitable alternatives to saccharin. Therefore, continued availability of saccharin is necessary in order for the OTC medicines industry to continue to provide a wide array of products which are demanded by and important to the public.

The Proprietary Association appreciates the opportunity to comment on the legislation and requests that this statement be inserted in the official hearing record of the Senate Committee on Labor and Human Resources hearing conducted on April 2, 1985.

Thank you for consideration of our views.

Sincerely,

James D. Cope
President, The Proprietary Association

JDC/lm

SHERWIN
WILLIAMS

CHEMICALS

The Sherwin-Williams Company
501 Murray Road
Cincinnati, Ohio 45217
Phone (513) 242-3300

April 8, 1985

Honorable Howard M. Metzenbaum
140 Senate Russell Office Building
U.S. Senate
Washington, D.C. 20510

Re: April 2, 1985 Hearing on S. 484, to Amend the Saccharin Study and Labeling Act

Dear Senator Metzenbaum:

At the April 2 hearing of the Committee on Labor and Human Resources on S. 484, to amend the Saccharin Study and Labeling Act, you presented certain information regarding trends in U.S. consumption of saccharin, sugar, and aspartame (nutrasweete). A table was presented for viewing by the Senators and the public showing data in tons for each substance for each year from 1979 through 1984. I am writing to bring to your attention the fact that the figures presented on the chart for saccharin were not correct.

As you know, Sherwin-Williams is the only domestic manufacturer of saccharin. All the saccharin in the United States is either provided by Sherwin-Williams or by importers. Our production information is necessarily confidential and proprietary in nature and cannot be disclosed for the public record. However, using this information as well as our knowledge of imports of saccharin, we believe we can give you some indication of actual patterns and levels of consumption of saccharin in the United States, thereby indicating the factual problems with the information provided on the chart.

The data on the chart showed the following figures for saccharin use: 1979-- 832,870 tons; 1980-- 876,645 tons; 1981-- 920,000 tons; 1982-- 975,660 tons; 1983-- 1,113,875 tons; and 1984-- 1,184,500 tons for a total tonnage of 5,903,550 tons (5.9 million tons) over the six-year period of

1979-1984. In fact, a total of 54.1 million pounds or a total of only 27,050 tons of saccharin was either produced in or imported to the United States for that entire six-year time period. Thus the actual total tonnage of saccharin for the entire six-year time period is only 0.02 million tons. This is more than 30 times less than the lowest figure on the chart for one year (1979-- 832,870 tons) and is almost 300 times less than the total of the figures shown on the chart.

The data on the chart displayed at the hearing showed a steady increase in saccharin production from 1979-1984. Our information shows that from 1979 to 1981 there was a gradual decrease in total saccharin production. From 1982-1983 there was an increase in total saccharin production, followed by a decrease in 1984.

Therefore, not only are the actual figures on the chart for saccharin per year grossly out of line with the actual amounts of saccharin produced in or imported to the United States, but the trend in saccharin usage on the chart is misleading and not supported by the facts. The total amount of saccharin in the United States for the period 1979-1984 is about 27,050 tons (0.02 million tons); the highest amount in any one year is 5,800 tons (0.0058 million tons). In 1984 saccharin production began to decline and a gradual decline is continuing.

It is not clear to me what the figures on the chart are showing in regard to saccharin, but they cannot possibly be showing the actual amount of saccharin produced or available in the United States for the time period indicated.

We hope that this information is of some assistance to you and we request that this letter be included in the hearing record.

Sincerely,

Kenneth H. Wilkinson

Kenneth H. Wilkinson
Director of Industry and
Government Affairs

KHW:Kakl
cc: Senator Orrin Hatch
Members, Committee on Labor and Human Relations
James Waggoner
Doug Campbell, Esq.
Robert Taft, Jr., Esq.
Joan M. Kovalic, Esq.

PUBLIC VOICE
FOR FOOD & HEALTH POLICY

1001 Connecticut Avenue, N.W.
Suite 522
Washington, D.C. 20036
202 659-5930

STATEMENT OF
PUBLIC VOICE FOR FOOD AND HEALTH POLICY
IN CONNECTION WITH
HEARINGS HELD ON APRIL 2, 1985 BEFORE
THE COMMITTEE ON LABOR AND HUMAN RESOURCES
OF THE UNITED STATES SENATE
REGARDING SACCHARIN

Mr. Chairman, as members of this committee know, we at Public Voice for Food and Health Policy have long been concerned about the risks posed to the health of consumers by the use of saccharin. Public Voice for Food and Health Policy is a non-profit consumer research education and advocacy organization which specializes in food safety, nutrition and agricultural policy. The reasons for our concern can be readily stated.

Each year consumers drink over $4 billion worth of diet soft drinks, the majority of which contain saccharin. In addition, Americans spend many times that amount on other products containing saccharin. Clearly, then, saccharin plays an important role in the American diet.

That being so, it is disturbing that saccharin has been authoritatively shown to cause cancer in laboratory animals. Ordinarily such findings would require the Food and Drug Administration (FDA) to ban saccharin pursuant to the Delaney Clause of the Food, Drug and Comestic Act, and indeed in 1977 FDA proposed to do exactly that. Only imposition and repeated extension of a Congressional moratorium have kept saccharin on the market. S. 484 would now extend that moratorium for an additional three years.

We oppose the three-year extension for several reasons. First, and fundamentally, it would increase the level and duration of the public's exposure to the carcinogenic risks posed by saccharin.

Second, the three-year extension would significantly deepen the precedent established by the moratorium--that our nation's commitment to removing cancer-causing substances from our foods is less than complete. There is a real danger that these extensions will become routine, as has happened in other food safety programs administered by FDA[1], and that, in other words, the exception will begin to swallow the rule.

To prevent this from happening, extensions of the moratorium must be given reluctantly, after all other alternatives have been reviewed and rejected, and must be restricted to the shortest time period needed. We believe that the Committee's action in holding the April 2nd hearing is a step in this direction, and we commend the Committee for not treating the three-year extension proposal as simply a routine matter.

Based on the testimony presented at the hearing and other available information, we conclude that a three-year extension has not been shown to be needed at this time. What is needed now is for FDA to make a broad re-evaluation of the alternative artificial sweeteners, including saccharin, aspartame, cyclamates, and the newer additives, such as acesulfame-K. Substantial progress can be made on such a review during a one-year period. Accordingly, we recommend that any extension be limited to that period.

It should be taken into account, as Commissioner Young did at the April 2nd hearing, that once the moratorium expires, FDA will still require at least six months or, more likely, more than a year to fulfill the rulemaking requirements needed to impose any ban on saccharin. Thus, in practical terms, a one-year moratorium would give FDA two years or more to continue working on a subject with which it is already familiar. Given the possibility that the status of other artificial sweeteners may change during the next two years, and that these changes may affect the perceived need for saccharin, it would be imprudent for Congress to stay the mandate of the Delaney Clause for a longer period of time.

Enforcement

As a result of testimony and exhibits presented at the April 2nd hearing, the Committee will no doubt be inquiring into FDA's enforcement priorties related to saccharin. As consumer advocates, we at Public Voice take it as axiomatic that if FDA is prevented from banning a carcinogenic substance like saccharin, it at least ought to fully discharge its legal obligations to ensure that the public is alerted of these carcinogenic risks.

In particular, the Saccharin Study and Labeling Act requires that:

---

[1] We note, for example, that on April 2, 1985, FDA delayed for the 27th time a decision on whether widely-used food and drug dyes pose an unacceptable risk to the public. N.Y. Times, April 3, 1985, C10, Col. 5.

(a) Foods containing saccharin carry a label warning "in conspicuous and legible type in contrast by typography, layout, and color...," and

(b) that grocery stores display "prominently" two or three saccharin warning signs.

There is ample evidence that these requirements are not being followed and that FDA's enforcement program is inadequate. Commissioner Young's inability to reassure the Committee that FDA would promptly rectify this situation is alarming. It seems clear that unless Congress provides additional direction to FDA, the saccharin warning requirements will remain a dead letter. We urge the Committee to specifically address the enforcement issue in its report and to make clear that vigorours enforcement of warning requirements is a prerequisite to any extension of the saccharin moratorium.

Respectfully submitted,

Ellen Haas

Ellen Haas
Executive Director
Public Voice for Food
and Health Policy

April 11, 1985

COMMENTARY BY SEARLE FOOD RESOURCES, INC. ON STATEMENTS MADE BEFORE THE SENATE COMMITTEE ON LABOR AND HUMAN RESOURCES, SENATOR ORRIN G. HATCH, CHAIRMAN.

Aspartame has been demonstrated to be a safe food ingredient for the public. It was approved by the FDA after extensive preclinical testing by Searle and clinical testing at independent universities and medical centers. It also has been approved by the World Health Organization, the European Economic Community, and the regulatory agencies of over 40 countries throughout the world.

In Dr. Wurtman's testimony he restates the hypothesis which he first suggested two years ago: the consumption of large quantities of aspartame together with carbohydrates might result in changes in neurotransmitter activity in the brain and, therefore, in behavior. Leave aside, for the moment, the fact that it is unlikely that one would, as Dr. Wurtman suggests, ingest an aspartame-sweetened beverage with a pure carbohydrate, such as sugar. It is likelier to be taken with something like his much-cited example of a peanut butter and jelly sandwich. He fails to note that such a snack also contains a considerable amount of protein amino acids, which he says are needed to compete with phenylalanine for entrance into the brain.

Dr. Wurtman's hypothesis has been reviewed by the Food and Drug Administration, which concluded that "the ingestion of aspartame, either alone or in combination with high levels of carbohydrates, will not result in behavioral modification even under the dietary extremes cited in [Dr. Wurtman's] comment." (Federal Register, July 8, 1983).

His hypothesis was later reviewed by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the Department of Health and Social Security in the United Kingdom, which stated "categorically" that it saw,

> "no reason to change its previous conclusion about the safety of aspartame. After ingestion, aspartame is broken down to phenylalanine and aspartic acid: both are naturally occuring amino acids, and phenylalanine is essential to life. Evidence available shows that the use of aspartame as a sweetener does not raise levels of phenylalanine in the body significantly above the values seen when normal foods containing phenylalanine are consumed; it is therefore most unlikely that aspartame would have any effects on humans that would not be seen with common foodstuffs."

Most recently, Dr. Wurtman's hypothesis was considered by the Scientific Committee for Foods of the European Economic Community, which concluded that:

> "the data provided no evidence that the occasional transient changes in blood amino acid levels, following simultaneous ingestion of aspartame and glucose, could produce changes in neurotransmitter levels which might affect mood or behaviour."

In short, Dr. Wurtman's hypothesis has been carefully considered and thought to be irrelevant to the issue of safety by leading independent scientific review authorities. Dr. Wurtman's hypothesis will confuse the public because it does not distinguish changes in the chemistry of rat brain from what is known about the actual biochemical effects of aspartame in man, and in turn, from his suppositions about human behavior.

The Committee should also know that Dr. Wurtman fails to put his own chemical studies in rat brain into a balanced perspective. Those unacquainted with brain chemistry may not know that many ordinary foods and food constituents, including sugar itself and other amino acids of protein, can alter the amino acid composition of the brain of laboratory rats (1). Some may infer, from Dr. Wurtman's statement, that these changes are abnormal and potentially dangerous. There is no evidence that this is true. Such changes are expected and normal after the ingestion of foods, as Dr. Wurtman has demonstrated for a variety of nutrients in his own laboratory (2).

Dr. Wurtman goes on to say that when man consumes aspartame in high doses but "within the FDA's estimates of 90th percentile intakes -- blood amino acid levels change in ways that almost certainly produce corresponding alterations in the chemical composition of their brains." He agrees that the changes in man would be different from those in the rat because of known differences between man and the rat in the way they metabolize phenylalanine (an amino acid constituent found in all proteins). However, he does not point out that aspartame ingestion at this level gives no greater increase in blood levels of phenylalanine than those following a meal including a hamburger and milkshake (3).

Dr. Wurtman says that these blood amino acid changes in man "almost certainly produce corresponding alterations in the chemical composition of their brains". We do not agree that this must occur. On the contrary, human plasma amino acid date provided by Dr. Stegink suggest that such changes in amino acid composition in brain would not occur (3).

Going from observations in rat brain to a presumption about what happens in human brain (which flies in the face of the actual evidence on blood levels in man), Dr. Wurtman then asserts that "it seems likely that aspartame in doses of sufficient size, will affect brain function and behavior in people..." There is no present scientific evidence that aspartame alters behavior in man. This is true even at the extraordinary level of intake Dr. Wurtman mentions. This problem now has been systematically studied in three different laboratories, including one at the NIH. No difference in behavior was found between subjects given aspartame and those given sugar or saccharin (4-6). In fact, differences in behavior do not occur in rats fed enormous doses of aspartame daily for three months (7).

Dr. Wurtman then supports his speculations about what happens in human brain with a misinterpretation of the conclusions of the anecdotal case reports analyzed by the CDC. The major conclusion of the CDC report to the FDA is that there is no "evidence for the existence of serious widespread adverse health consequences attached to the use of aspartame". This was affirmed in Dr. Trowbirdge's testimony before this committee. Dr. Wurtman neglects to point out that the clinical studies were proposed by the CDC in order to rule out the possibility that there may be some individuals with an "as yet undefined sensitivity" to aspartame, rather than because it represents a general health hazard. While there is no scientific evidence that such a subset of hypersensitive people exists, Searle has funded such an FDA-approved study at an independent community medical center.

Finally, following the testimony of Dr. Howard Roberts, Vice President for Science and Technology , of the The National Soft Drink Association, Senator Metzenbaum questioned Dr. Roberts about a draft (August 8, 1983) of a petition to the FDA for a hearing. The basis of concern expressed in that draft was the stability of aspartame in soft drinks and the work of Wurtman discussed above.

In the Searle Petition for Aspartame-Sweetened Carbonated Beverages, the amount of aspartame remaining after storage was studied. The sum of aspartame and its conversion products found after storage did not equal the quantity of aspartame at the start. Questions were raised about the identity and safety of the missing material. In fact, all of the currently known conversion products had been identified in that petition. However, the question was raised whether some were measured with methods sufficiently accurate to ensure quantification.

The FDA considered identical allegations twice in the course of approval of the Aspartame-Sweetened Carbonated Beverage Petition, and twice dismissed them as unsubstantiated.

Questions regarding these conversion products have since been resolved. Using validated analytical methods, several simulated and actual beverages systems were evaluated during storage at elevated temperature (40°C). No heretofore unidentified products are formed as the beverages aged, and the new method provides recoveries of 98-100% of all materials. All the materials found had been known by Searle and the FDA. Studies have shown that at a point of about 50% APM conversion, a beverage product has lost sufficient sweetness that its taste is unacceptable. At this point, no single conversion product predominates.

Finally, we would agree that Dr. Wurtman's endorsement of "the continued general use of aspartame" by the public is entirely appropriate.

REFERENCES

1. Wurtman, R.J. Nutrients That Modify Brain Function. 1982. Sci. Amer. 246: 42-51

2. Wurtman, R.J. Behavioral Effects of Nutrients. 1983. Lancet, 1: 1145-1147.

3. Stegink, L.D., Filer, L.J., and Baker, G.L. 1981. Plasma and Erythrocyte Concentrations of Free Amino Acids in Adult Humans Administered Abuse Doses of Aspartame. J. Tox. Env. Hlth., 7: 291-305.

4. Wolraich, M., Millich, R., Stumbo, P. and Schultz, F. 1985. Effects of Sucrose Ingestion on The Behavior of Hyperactive Boys. J. Pediatrics (in press)

5. Ferguson, H.B. The Effects of Sugar and Aspartame on Children's Cognition and Behavior: A Challenge Study. Presented at the "Diet and Behavior: A Multidisciplinary Evaluation Symposium". November 27-29, 1984; Nutr. Reviews (in press).

6. Rapoport, J.L. Diet and Hyperactivity. Presented at the "Diet and Behavior: A Multidisciplinary Evaluation Symposium". Nov. 27-29, 1984; Nutr. Reviews (in press).

7. Potts, W.J., Bloss, J.L., and Nutting, E.F., 1980. Biological Properties of Aspartame, I. Evaluation of Central Nervous System Effects. J. Environ. Pathol. Toxicol. Vol. III, pp. 341-353.

JUVENILE DIABETES FOUNDATION

TESTIMONY ON S. 484

The Juvenile Diabetes Foundation (JDF) appreciates this opportunity to submit its views regarding S. 484, a bill to extend The Saccharin Study and Labeling Act. JDF is an international voluntary health organization of over 160 chapters dedicated to furthering research in diabetes and improving the quality of life of diabetics. As the largest organization of diabetic consumers in the world, JDF is uniquely concerned with the benefits and risks of non-nutritive sweeteners.

Since FDA's original proposal to ban the use of saccharin, JDF has been an active and vocal participant in the national debate over the availability of artificial sweeteners. During initial consideration of the ban, JDF testified before Congressional committees highlighting the adverse physical and emotional effects that such a ban could have on insulin-dependent diabetics and other individuals, who, for various reasons, must use artificial sweeteners. Since that time, JDF has supported the extension of the moratorium on three separate occasions. While some of the reasons for our original position have been obviated by intervening events during the past seven years, including the approval of aspartame, JDF continues to support the extension of the moratorium.

Other non-nutritive sweeteners should also be made publicly available, subject to rigorous scrutiny by the Food and Drug Administration (FDA). Continued investigation of the side-effects of artificial sweeteners now on the market should be encouraged by the Federal government. In order to insure the impartiality of the results, studies should be conducted under the auspices of the FDA, the National Institutes of Health (NIH) and the Centers for Disease Control (CDC). In the meantime, warnings of potential danger which appear in stores and on products containing any of the artificial sweeteners should be continued, and efforts should be made to ensure that consumers are aware of these warnings. Ultimately, the decision as to whether a diabetic child should use any artificial sweeteners is a decision which must be made by the child's parents.

Because the insulin-dependent, or juvenile diabetic is required to control his intake of sugar and thus his blood sugar levels, a very carefully crafted diet must be developed. Although individualized, a diet becomes a very social activity -- particularly for a youngster in school. Passing up candy corn at Halloween, birthday cakes with sugared frosting and milkshakes at McDonald's are the kind of deprivations a diabetic child must endure throughout childhood. Such restrictions become the potential source of those all-important differences that separate the diabetic child from his peers.

This self-denial, when coupled with the requisite daily insulin injections and the frequent pricking of fingers for blood sugar tests can create a world that seems alien and hostile to the young diabetic.

But the availability of artificial sweeteners has softened this world, easing social situations for the diabetic child and allowing him to more easily accept and deal with his disease. While natural foods are far preferable, the realities of the commercial world and the pressures of peer groups make diet drinks and artificially sweetened products acceptable alternatives. Moreover, such diet foods provide the diabetic with the ability to control the intake of sugar when circumstances conspire to force one off the established diet. Thus, recommendations to completely remove saccharin or any other substitute sweetener should take into account the impact this would have on the daily life of the juvenile diabetic.

Currently the diabetic child and his parents do have the option of choosing among a number of different artificial sweeteners. Saccharin, the subject of S.484, was discovered, in 1879 and remained the only artificial sweetener for over half a century. Cyclamates, the next artificial sweetener on the market, was discovered in 1944, but was banned in 1969 by the U.S. Department of Health, Education and Welfare. In 1981, aspartame received FDA approval for use in dry foods. Under its brand name, Nutrasweet, aspartame has achieved a great deal of popularity as a soft drink sweetener following FDA approval for such use in 1983. In 1982, Abbott Laboratories petitioned the FDA to reconsider its position on cyclamates. With FDA's decision due this year, it is possible that this third sweetener may reenter the marketplace in the future. Additionally, a new product acesulfame K is under FDA review following a petition filed by the American Hoechst Corporation.

The Juvenile Diabetes Foundation supports the availability of a variety of artificial sweeteners. No one product necessarily meets the need for artificial sweeteners in all forms, as these sweeteners are not completely interchangeable. Aspartame, for instance, loses it sweetness when heated and is thus an unacceptable additive for cooking and baking and in foods that require heat processing. For similar reasons, aspartame may not be acceptable for use in fountain soft drinks or in soft drinks that cannot necessarily be stored under cool conditions.

Perhaps, the most important reason, however, for the availability of a variety of non-nutritive sweeteners is the reduction of exposure. As more alternative artificial sweeteners become available, the consumer is increasingly exposed to smaller quantities of a single sugar substitute. Indeed, many diet soft drinks may include combinations of sugar approved substitutes. This is particularly critical as some of the questions regarding the impact of those various substitutes remain unanswered.

In 1977, scientific research raised enough serious questions about the safety of saccharin that the FDA announced its intention to ban the substance. Congress reacted with its moratorium, which also mandated further study of the issue. As a result, the National Academy of Sciences (NAS) conducted a review of the relevant scientific literature. Despite the findings of the NAS, the results of an investigation conducted by the National Cancer Institute in conjunction with the FDA, and the research of other outside investigators, some important questions remain unanswered. On balance, however, these recent investigations lead us to conclude that the concerns raised prior to 1977 regarding the carcinogenicity of saccharin may be less immediate than previously supposed. At the same time, recent allegations regarding the neurological impact of aspartame have suggested that neither sugar substitute has a completely clean bill of health.

Safety remains a preeminent concern, particularly to the parents of children who tend to utilize artifically sweetened products to a significant extent. Yet, the issue ultimately comes down to one of choice. It is, after all, the parents of the diabetic who must decide whether or not to use sugar substitutes as part of the approach to help control diabetes. We support the continuation and possible enhancement of warnings regarding the potential carcinogenicity of saccharin and the adverse effects of aspartame. Moreover, we advocate continued investigation and monitoring of the impact of products containing these substances on the safety of users. However, pending new scientific developments, we believe that the benefits of product variety may outweigh the detriment posed by forced consumption of a single additive in large quantities. Accordingly, we recommend that the Committee report out and Congress approve the limited extension of the saccherin moratorium as embodied in S.484.

STATEMENT OF

FRED WERTHEIMER, PRESIDENT

COMMON CAUSE

We appreciate the opportunity to submit to the record a copy of our 20 page investigation of the Food and Drug Administration's approval of aspartame.

In our investigation we found such serious deficiencies in the FDA's process of approving aspartame that we believe only a Congressional investigation can resolve all of the questions raised regarding aspartame and about the way in which the FDA carries out its approval process responsibilities.

We believe it is incumbent upon Congress to explore this matter, and we urge your committee to do so.

CommonCause

For Release: IMMEDIATE

Tuesday, July 10, 1984

For Information: Virginia Sassaman

STATEMENT OF COMMON CAUSE PRESIDENT FRED WERTHEIMER

CONGRESS SHOULD INVESTIGATE FDA'S DECISION TO APPROVE ASPARTAME

We are holding this press conference today to release the results of an investigation by Common Cause Magazine into aspartame -- the new low-calorie sweetener being marketed as NutraSweet -- and the process by which the Food and Drug Administration (FDA) approved it for use by the public. The investigation was conducted by Florence Graves, Common Cause Vice President for Publications and Editor of Common Cause Magazine.

After months of work, our investigation has found such serious deficiencies in the Food and Drug Administration's process of approving aspartame that we are calling on Congress to begin its own investigation of this approval process immediately.

In 1981, then FDA commissioner Arthur Hull Hayes approved aspartame for use in dry foods such as cereals and powdered drinks. In 1983, he extended the approval to soft drinks, which has greatly expanded consumption of the sweetener. This decision was the culmination of a controversy over aspartame that began at the FDA in 1974.

Among the matters that Congress needs to look at, we believe, are the following:

o How could the FDA reasonably conclude that the tests submitted by G.D. Searle & Co. establish that aspartame is safe? A number of these were so poorly conducted that former FDA commissioner Dr. Alexander Schmidt described the work as "reprehensible" in an interview with Common Cause Magazine.

o FDA scientists who initially reviewed the 13 tests Searle submitted to establish whether aspartame could cause genetic damage found serious deficiencies in all these tests, according to memos in the public record. Nevertheless, FDA officials decided the tests were good enough to rely upon in establishing aspartame's safety, according to documents from a 1980 scientific Public Board of Inquiry convened by the FDA.

How does the FDA justify this decision?

Common Cause Magazine asked Dr. Marvin Legator -- who helped pioneer mutagenicity testing at the FDA, where he worked from 1962 to 1972 -- to review the FDA's review of these 13 Searle tests. Dr. Legator is professor and director of environmental toxicology at the University of Texas medical branch in Galveston. Although Dr. Legator says he has "no reasons to suspect that aspartame would be active," he says all the tests are "scientifically irresponsible" and "disgraceful." He told Common Cause Magazine, "I'm just shocked that that kind of sloppy [work] would even be sent to FDA" and that FDA administrators accepted it.

o The 1980 Public Board of Inquiry convened by the FDA recommended that aspartame not be approved and that further tests be conducted because it believed there were still questions about whether aspartame could cause cancerous brain tumors. In addition, internal FDA documents obtained by Common Cause Magazine show that a number of significant deficiencies in the three pivotal tests used to determine whether aspartame might cause cancerous brain tumors were brought by FDA scientists to the attention of those advising Hayes during his deliberations in 1981, yet he decided to approve aspartame anyway.

On what basis could commissioner Hayes reasonably conclude it was all right to ignore the recommendations of the Public Board of Inquiry and of FDA scientists and instead approve aspartame for use in dry foods as he did in July 1981?

o According to Dr. Walle Nauta of the Massachusetts Institute of Technology (MIT), who headed the 1980 Public Board of Inquiry, FDA officials left him believing at that time that aspartame would not be used in soft drinks. Dr. Nauta told Common Cause Magazine that the Public Board of Inquiry's decision "specifically excluded use in soft drinks" and that he "definitely" would have wanted to look more closely at other tests and factors if he had known that soft drink use was being anticipated. In addition, Dr. Nauta says that questions raised after the Public Board of Inquiry by MIT's Dr. Richard Wurtman about aspartame's potential to affect brain chemistry -- and therefore behavior -- need "extensive testing." Such testing has not been required by the FDA. Nauta told Common Cause Magazine that aspartame "may be harmful in the long run."

Why wasn't the 1980 Public Board of Inquiry asked to look at the soft drink question and what are the consequences of its failure to make that evaluation? Why did the FDA dismiss preliminary tests done by Dr. Wurtman raising questions about the sweetener's potential effects on brain chemistry?

As a result of these and other serious questions raised in our investigation, we do not see how the FDA could reasonably conclude that Searle had met its burden under the federal law to establish "to a reasonable certainty" that aspartame is safe.

During the course of the 10-year controversy surrounding aspartame, questions have been raised by a number of scientists and others concerned with this sweetener's approval. A series of media stories have focused on health concerns and the controversial history of the testing. We think, however, that our investigation takes this story to a new level, revealing serious flaws in the process that the FDA used to approve this product. That's why we are asking Congress to investigate and make its own judgment as to whether the FDA properly carried out its responsibilities when it approved this sweetener for consumption by the American people.

Because this controversy has covered more than 10 years, our investigation is long and detailed. Given the extent and nature of the controversy, obviously all we can do at this press conference is give you the major highlights. We urge all of you to read this entire investigation as part of reporting on our findings.

# # #

CommonCause

For Release: IMMEDIATE
Tuesday, July 10, 1984

For Information: Virginia Sessaman

STATEMENT OF FLORENCE GRAVES, VICE PRESIDENT FOR PUBLICATIONS AND EDITOR OF COMMON CAUSE MAGAZINE

RESULTS OF COMMON CAUSE MAGAZINE INVESTIGATION OF FDA'S APPROVAL OF ASPARTAME

The FDA controversy concerning aspartame began in 1974, when two critics — consumer attorney James Turner and Dr. John Olney, professor of neuropathology and psychiatry at Washington University School of Medicine in St. Louis — challenged the initial 1974 FDA approval of aspartame, saying they believed the sweetener might cause brain damage. But before they could get a hearing on their complaints, an FDA scientist discovered discrepancies in Searle's report on testing of a drug called Flagyl. Searle's response to questions about the discrepancies only raised additional questions about Searle's testing.

Finally, in 1975, then FDA commissioner Dr. Alexander Schmidt took the unusual step of commissioning a special task force to investigate about 25 key tests Searle had submitted on seven products, including 11 tests on aspartame. That investigation brought into question all of Searle's tests between 1967 and 1975, former FDA commissioner Schmidt said in congressional hearings, including pivotal tests by Searle that were eventually used as part of the basis for the 1981 and 1983 FDA approvals of aspartame.

Among the task force's conclusions about Searle's testing was the following finding: "At the heart of the FDA's regulatory process is its ability to rely upon the integrity of the basic safety data submitted by sponsors of regulated products. Our investigation clearly demonstrates that in the G.D. Searle Co., we have no basis for such reliance now."

Under federal law, the manufacturer of a food additive — in the case of aspartame, G.D. Searle & Co. — has the burden of proving to the satisfaction of the FDA that there is a "reasonable certainty" that a food additive is safe. The FDA does not have to prove that it is harmful. Furthermore, if tests are inconclusive, an additive is not supposed to be approved by the FDA.

The vast majority of the tests — 90 of 113 entries — submitted by Searle to establish that aspartame is safe, were submitted in the early to mid-1970s, the period when Searle's testing was called into question by the FDA special task force. All aspartame tests that have ever been described by the FDA as "pivotal" were conducted during this period.

The special task force's findings about Searle's testing were so serious that they led the FDA general counsel to request a grand jury investigation of Searle. (The grand jury probe was later dropped.) Mr. Philip Brodsky, the lead investigator for the 1975 task force, told Common Cause Magazine he had "never seen anything" as "bad" as Searle's testing.

Dr. Schmidt, who served as FDA head at the time, said in an interview with Common Cause Magazine that Searle's testing was "incredibly sloppy science." He also said "what was discovered was reprehensible."

Schmidt also said that a pivotal test is one that is so important that it must be repeated if found invalid. The important question, Schmidt said, is: "Were there new pivotal experiments?"

The Common Cause investigation found that only one test ever described as pivotal by the FDA was repeated, and the FDA later said it was not used in the agency's safety assessment.

Given that the bulk of Searle's aspartame tests — including the pivotal tests -- had been called into question, the FDA at this point could have required Searle to repeat these tests. It did not.

Instead, over the period from 1977 to 1980, three further reviews of aspartame were undertaken under the auspices of the FDA. The first, by another special FDA task force, examined three of the pivotal aspartame tests submitted by Searle and found a number of problems with the tests. This study is known as the Bressler Report, after FDA team leader Jerome Bressler. In particular, the Bressler team looked at one pivotal test done to help establish that aspartame wouldn't cause cancerous brain tumors. About this test, Bressler told Common Cause Magazine, "you don't have to be brilliant to know...it was a lousy study; it was a sloppy study." The second review was conducted by a group of pathologists known as the Universities Associated for Research and Education in Pathology (UAREP). The UAREP review examined 12 pivotal studies, and, like the 1975 task force investigation, this review has been at the heart of the current controversy over Searle's aspartame tests. While the FDA has tried to use this review as evidence that the questionable Searle tests are valid, we believe that our investigation shows that the UAREP review does not establish the validity of Searle's tests.

In the words of then commissioner Arthur Hull Hayes in his 1981 decision, UAREP was to "make sure that the studies were actually conducted."

UAREP found that Searle had not misrepresented the test data that had been reported, but UAREP has confirmed to Common Cause Magazine that it did not do an in-depth investigation of how the tests were actually conducted.

In an interview with Common Cause Magazine, Dr. Kenneth Endicott, then as now director of UAREP, agreed that UAREP's conclusions did not mean that Searle's tests were valid. He said, "there were lots of other opportunities for error," — errors that would not have been in the record UAREP reviewed. In fact, as noted, the 1975 task force found the Searle tests inadequate in a number of areas.

UAREP, for example, did not take responsibility for a number of aspects important to the way the studies were conducted — including animal care, lab practices and homogeneity of feed. UAREP also said its conclusions "are not necessarily representative of other Searle studies."

UAREP also did not evaluate the designs of the tests, another important factor in determining validity. The 1975 FDA task force had found problems in the designs of some aspartame tests.

Both the 1975 task force and UAREP raised questions about whether the test substances — aspartame and DKP — were uniformly mixed in the animals' feed and whether the test substances were "stable" — that is, didn't deteriorate significantly over time. Both groups said these factors are important to the interpretation of the test results, and both concluded that these issues were not resolved. The task force said that because of inadequate practices at both Searle and its major contractor, "there is no (italics theirs) way in which it can be assured that animals received the intended dosages."

At this point, the FDA was left with the following issues:

o The 1975 FDA task force had looked at a number of the pivotal tests and raised questions about all of Searle's tests — including the vast majority of the aspartame tests — done between 1967 and 1975.

o The Bressler team had reviewed three pivotal tests and found a number of problems with those tests.

o The designs of the tests apparently had not been reviewed by the FDA's Bureau of Foods since the tests had been submitted for the 1974 approval. The 1975 task force said it found problems in the designs of some aspartame tests.

o UAREP had verified that 12 pivotal tests had been conducted, and that few, if any, of the discrepancies that the pathologists found would have changed the statistical results of the tests. But UAREP says it was told by both Searle and the FDA not to evaluate the designs, so "any interpretation of results applies only to the experiments as designed." As previously pointed out, UAREP also did not take responsibility for a number of aspects important to the way the studies were conducted — including animal care, lab practices and homogeneity of feed. UAREP also said its conclusions "are not necessarily representative of other Searle studies."

o The FDA's Bureau of Foods relied upon a number of tests called into question by the 1975 task force investigators which were not reviewed by either the Bressler team or UAREP, according to 1980 Public Board of Inquiry documents. That leaves unanswered questions about how the FDA determined the tests were valid.

How did the FDA take all these factors into account when it decided that the Searle tests were good enough to rely upon?

Our investigation found no evidence in the public record that the FDA successfully reconciled these factors. Nevertheless, the FDA decided the tests were good enough to rely upon, and in 1980, a Public Board of Inquiry was established to examine certain key health concerns that had been raised about aspartame by critics Turner and Olney.

Once again, the manner in which the Searle tests were conducted was not examined. Even though Turner and Olney said there were questions about the way the studies had been done, Dr. Walle Nauta, who headed the board, said he believed the board's job was to interpret the results of the tests. Nauta said the board had to assume that the tests had been well-conducted. Nauta told Common Cause Magazine that the board had "concern about the validity of a number of the [test] data." "It was a shocking story we were told" about the history of Searle's testing, but "there was no way we could go after it. We had absolutely no way of knowing who was right. We had to take the FDA's word."

Even though the Public Board of Inquiry accepted the tests as valid, it still concluded that the issue of brain tumors had not been conclusively resolved and called for further tests.

Thus, when commissioner Hayes came to make his decision shortly after assuming office in 1981, he was faced with a public record that included a series of Searle tests called into question by the 1975 task force — tests that had not been established to be valid in terms of their design or conduct, according to the public record. He also was faced with a Public Board of Inquiry recommendation for further tests on the brain tumor issue.

Our investigation shows that a number of the questions concerning the aspartame tests were brought to the attention of those advising former FDA commissioner Hayes.

One FDA official privy to deliberations made at Hayes' level told Common Cause Magazine that the "people at the top" were not receptive to important concerns raised about the quality and validity of some of the key tests submitted in support of aspartame. "Real questions" about the reliability and interpretation of data "were glossed over" at the commissioner's level, according to this official. He added that Hayes and his close associates wanted FDA scientists to concentrate on providing rationales for overturning the 1980 Public Board of Inquiry instead of focusing on the fact that there were unresolved questions about key tests.

As a result of these and other serious questions raised in our investigation, we do not see how the FDA could reasonably conclude that Searle had met its burden under the federal law to establish "to a reasonable certainty" that aspartame is safe.

Other highlights of the investigation:

o Internal FDA documents obtained by the magazine show that a number of significant deficiencies in the three pivotal brain tumor tests were brought by FDA scientists to the attention of those advising Hayes during his deliberations, yet he approved aspartame anyway.

A draft memo to Hayes reads, "As you know, this is a subject upon which competent, neutral scientists have disagreed. The [FDA] Bureau of Foods found aspartame approvable on these grounds. The Public Board of Inquiry found it not approvable without further testing. Your final decision, therefore, will largely reflect a policy judgment on how certain you want to be...."

o In 1973, the FDA's Bureau of Foods asked the FDA's Bureau of Drugs to evaluate 10 tests on humans submitted by Searle to determine "whether safety problems might be anticipated should this sweetener be marketed for general use." Memos show that Dr. Martha Freeman, then of the Bureau of Drugs, concluded that "the information provided is inadequate to permit an evaluation of potential toxicity of aspartame."

Freeman recommended that "marketing for use as a sweetening agent should be contingent upon satisfactory demonstration of clinical safety of the compound," which she said required more rigorous testing. The Bureau of Foods rejected her recommendations and has continued to cite these 10 studies as evidence of safety.

o The FDA continues to maintain that aspartame poses no risk for children or infants, but documents obtained by Common Cause Magazine show that as early as 1974 and as late as 1980, some FDA officials believed it might be advisable to require a warning that aspartame should not be fed to infants.

In 1980, for example, the FDA said, "in consideration of the remote possibility that a parent might use aspartame as a non-sugar sweetener in the infant formula or food, there may be some merit in the inclusion of a statement on the label to the effect that aspartame and aspartame-containing foods are not intended for use in infant feeding."

When Dr. C.J. Kokoski of the FDA's Division of Toxicology was recently asked why the FDA didn't require a notice to warn parents not to feed aspartame to infants, he said it is unlikely that parents would feed aspartame to infants. He also said that even if they did feed infants aspartame, it would not pose problems.

o Although Searle and the FDA frequently point to the fact that aspartame has been approved in more than 30 countries as evidence that it is safe, Robert Shapiro — head of Searle's NutraSweet division — told Common Cause Magazine that approval in these foreign countries was based "essentially" on the same controversial tests also submitted to the FDA.

Our investigation has found that a number of scientists have raised questions about the sweetener's safety, and that a number of Americans have alleged that they have experienced side effects when consuming aspartame. Our investigation has also found that the expanded use of aspartame in soft drinks — even if the tests in question had been determined to be valid — has raised a number of important questions among some scientists and others.

Under the Freedom of Information Act, Common Cause Magazine obtained copies of about 600 complaints about aspartame from the FDA's files. In these complaints, people allege that they have suffered headaches, dizziness, rashes, menstrual problems and seizures after consuming foods and drinks containing NutraSweet. The complaints, most of which were received this year, are being investigated by the federal Centers for Disease Control in Atlanta. We have been told their findings are expected this month.

Dr. Walle Nauta, chairman of the 1980 Public Board of Inquiry convened by the FDA to examine concerns that aspartame wouldn't cause brain damage or brain tumors, told Common Cause Magazine he was surprised by the FDA's approval of aspartame for use in soft drinks. Nauta said the board's review "specifically excluded use in soft drinks." "We were told by the FDA that aspartame in solution has limited life....We took the whole conversation to mean it was unlikely [to be considered as a sweetener] in bottles or cans."

Nauta said he "definitely" would have conducted the Public Board of Inquiry's review differently if he had known there were plans to use aspartame in soft drinks. "We certainly would have had to look at other things," such as "what happens in the breakdown process." Aspartame is known to break down in heat and in solution — especially acidic solution — into chemicals such as DKP and methyl alcohol. (It also loses its sweetness over time.)

o According to a draft objection obtained by Common Cause Magazine, within two weeks before aspartame was approved for soft drink use, the National Soft Drink Association (NSDA) appeared to have had enough concerns about the safe use of aspartame in soft drinks that it considered formally submitting an objection to the approval.

NSDA science director Dr. Robert McQuate says the association didn't file the objection because all safety concerns were totally resolved. But a lengthy magazine interview with McQuate leaves a number of troubling questions.

The questions being raised by various scientists about the expanded use of aspartame in soft drinks include the following:

o Did the FDA fail to recognize the possibility that large amounts of aspartame, especially when consumed with carbohydrates, may affect brain chemistry and therefore behavior? Dr. Richard Wurtman, professor of neuroendocrine regulation at MIT, has said his preliminary tests indicate that this is a possibility. The FDA has dismissed Wurtman's initial research, which he presented prior to soft drink approval, saying his hypothesis is not supported by his data. Dr. Nauta, of the 1980 Public Board of Inquiry, and Dr. McQuate, of the National Soft Drink Association, have told Common Cause Magazine that Wurtman's hypothesis warrants further testing. Nauta said, "Dr. Wurtman may be right." Aspartame "may be harmful in the long run."

o Did the FDA significantly underestimate consumption of aspartame by the American public? Dr. William Pardridge, associate professor of medicine at the University of California at Los Angeles, wrote to the FDA last year, saying he believed that the FDA did underestimate consumption and cited figures showing how children eating aspartame-sweetened foods at breakfast, lunch and as snacks, could be well on their way to consuming the maximum amount of aspartame the FDA used as the basis for its safety assessment. Pardridge also said that instead of asking whether aspartame could cause brain damage, the FDA should have asked whether high-dose aspartame use would "cause subtle changes in brain development." He pointed to the possibility that women with an intolerance to phenylalanine — one of the major components of aspartame — who consumed large amounts of aspartame while pregnant, might give birth to infants with "a 10 or 15 percent" drop in expected IQ levels. He estimates that there are "20 million individuals in the country with a phenylalanine intolerance," many of whom may be unaware of their condition.

o Did the FDA fail to address adequately questions of safety raised by aspartame's decomposition products, among them DKP (diketopiperazine) and methyl alcohol (methanol)? Consumer attorney James Turner, representing the Community Nutrition Institute, and others believe that safety concerns about these chemicals have not been adequately addressed.

The American people have no choice but to depend upon the federal government to assure them that chemicals added to their foods are safe. Poll after poll shows that the American people expect the government's Food and Drug Administration to carry out this responsibility.

In the case of NutraSweet, our investigation has found that the government has failed the public. That's why we are calling upon Congress to begin an investigation of the FDA's approval of NutraSweet. Today we are delivering letters to all members of the House Energy and Commerce Committee and the Senate Labor and Human Resources Committee, asking them on the basis of our findings to begin their own investigation immediately.

The CHAIRMAN. I just want to thank everybody for attending. It has been a long hearing, but it has been an essential hearing, and I think we have excellent testimony here today.

With that, we will recess until further notice.

[Whereupon, at 6:26 p.m., the committee recessed, to reconvene at the call of the Chair.]

○